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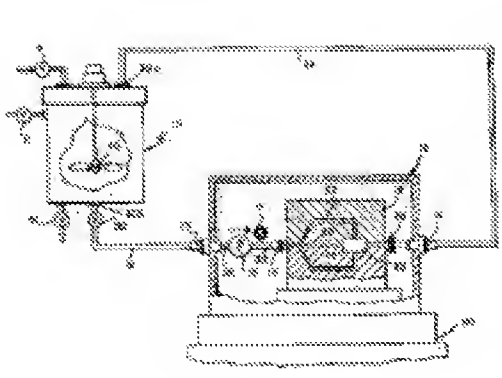
(54) **METHOD AND APPARATUS FOR HOMOGENIZING AEROSOL FORMULATION**



(57)Abstract:
PROBLEM TO BE SOLVED: To homogenize and atomize aerosol formulation by a method in which a homogenizer equipped with an interaction chamber and a pressure increasing pump and a reactor are connected with each other by a fluid conduit by a closed loop, and aerosol formulation components, after being made to flow separately, are recombined.
SOLUTION: A mixing container 10 equipped with a mixing means 40 and a high pressure homogenizer 12 are connected by conduits 31-34 and connectors 30a, 30b into a closed loop. All aerosol formulation is placed in the container 10, pressurized, and mixed by a stirrer 40. When an outlet value 50 is opened, it flows in the connector 30b and the homogenizer 12, and returns to the container 10 from the connector 30a. The homogenizer 12 is equipped with an interaction chamber 18 and a pressure increasing pump 15. In the chamber 18, after aerosol formulation components being split into two flows by a splitter 20, the flows are recombined in an impaction chamber 28, and the aerosol formulation is homogenized. The formulation containing a low boiling point jetting agent is homogenized in this way.

CLAIMS

[Claim(s)]
[Claim 1]A mixing vessel; Have a homogenizer arranged by carrying out fluid communicating to said reaction vessel, and said homogenizer is provided with an interaction room and a booster pump, and said interaction room A flow splitter, With said flow splitter, have an impaction room which makes a flow of said mixture diversion of river recombine, and said booster pump, . In order to make said mixture uniform in the case of said recombination of said flow, had a gas compressor style which propels said flow in said impaction room, and have been arranged between the; aforementioned reaction vessel and said homogenizer. Closed equipment provided with a fluid lead pipe which forms closed equipment among them, and; which uniforms a mixture containing at least one low boiling point components.
[Claim 2]The closed equipment according to claim 1 which said interaction room is further provided with the 1st infinitesimal channel and the 2nd infinitesimal channel, and is characterized by arranging each of said 1st and 2nd infinitesimal channels so that it may collaborate with said flow splitter and a flow of said mixture may be accepted.
[Claim 3]The closed equipment according to claim 2 which said 1st infinitesimal channel and said 2nd infinitesimal channel branch from said flow splitter, and is characterized by gathering in said impaction room.
[Claim 4]The closed equipment according to claim 2 which said 1st and 2nd infinitesimal channels are arranged so that fluid communicating may be carried out to said impaction room and a fluid may be supplied there, and is characterized by said impaction room having larger volume than volume of said infinitesimal channel.
[Claim 5]The closed equipment according to claim 1, wherein said closed equipment is further provided with the 2nd fluid lead pipe arranged between said homogenizer and said reaction vessel for supplying a uniformed fluid to said reaction vessel from said interaction room.
[Claim 6]it had further the 2nd pump arranged at said interaction room and parallel, and said 2nd pump was closed with said closed equipment via the 1st valve and the 2nd valve -- fluid communicating being carried out, and it being arranged and, The closed equipment according to claim 1, wherein said 1st valve is arranged at an entrance side of said interaction room and said 2nd valve is arranged at an outlet side of said interaction room.
[Claim 7]The closed equipment according to claim 1 which is further provided with a bypass valve arranged by carrying out fluid communicating to said reaction chamber, and is characterized by providing a channel for said mixture to circulate in said closed equipment in the case of an operation of said bypass valve.
[Claim 8]Closed equipment which uniforms aerosol pharmaceutical preparation, comprising: An agitating equipment means for mixing aerosol pharmaceutical preparation in a container means for accommodating two or more aerosol components of the drug product, and the; aforementioned container means; It has an interaction room means for uniforming said aerosol pharmaceutical preparation, A splitter means to carry out fluid communicating of said interaction room means to said container means, it to be arranged, and for said interaction room means make a flow of (1) aerosol components of the drug product divide into at least two flows.
(2) having an impaction means for making said at least two flows recombine with one flow --; -- making easy a transfer of a fluid from said container means to said interaction room means, and, The 1st fluid duct means for maintaining closed equipment among them; the 2nd fluid duct means for making easy a transfer of a fluid from said interaction room means to said container

means, and maintaining closed equipment among them.;

[Claim 9]The closed equipment according to claim 8, wherein said interaction room means is provided with an infinitesimal channel means for transporting said flow to said impaction means from said splitter means.
[Claim 10]The closed equipment according to claim 8 while said interaction room means is uniformed [said aerosol pharmaceutical preparation], wherein it performs an additional function which superfines-izes said aerosol pharmaceutical preparation.
[Claim 11]The closed equipment according to claim 8 which is further provided with a bit means for carrying out the bit of said aerosol pharmaceutical preparation to an aerosol can, and is characterized by carrying out fluid communicating of said bit means to said container means, and arranging it.
[Claim 12]The closed equipment according to claim 8 which is further provided with a bypass valve means for providing a channel for said aerosol pharmaceutical preparation to circulate through inside of said closed equipment, and is characterized by carrying out fluid communicating of said bypass valve means to said reaction vessel, and arranging it.
[Claim 13]a) A process of determining a desired level of uniformity;
b) A process of mixing aerosol pharmaceutical preparation in a reaction vessel;
c) A process which circulates said mixed aerosol pharmaceutical preparation with a high voltage homogenizer;
d) A process which operates said high voltage homogenizer by sufficient pressure to attain uniformity of said aerosol pharmaceutical preparation;
e) A method of uniforming aerosol pharmaceutical preparation with a closed continuation loop device under a high pressure by which is made to circulate through said aerosol pharmaceutical preparation, and it is characterized by repeating said said from process (b) to process (e) until it attains said desired level of a process returned into said mixing vessel, and; uniformity.
[Claim 14]How to uniform the aerosol pharmaceutical preparation according to claim 13, wherein said closed continuation loop device is pressurized up to about 689 kilopascals (100 psi).
[Claim 15]How to uniform the aerosol pharmaceutical preparation according to claim 13, wherein said high voltage homogenizer and a micronizer supply a pressure of about 55,158 to 62,053 kilopascals (from 8,000 psi to 9,000 psi) to aerosol pharmaceutical preparation.
[Claim 16]How to uniform the aerosol pharmaceutical preparation according to claim 13 repeating said process (d) 10 times from said process (b) of said method.
[Claim 17]How to uniform the aerosol pharmaceutical preparation according to claim 13, wherein said aerosol pharmaceutical preparation contains an active ingredient and a propellant.
[Claim 18]How to uniform the aerosol pharmaceutical preparation according to claim 17, wherein said active ingredient contains a superfines-ized compound.
[Claim 19]How to uniform the aerosol pharmaceutical preparation according to claim 18, wherein said active ingredient contains a respiratory compound of activity pharmaceutically.
[Claim 20]How to uniform the aerosol pharmaceutical preparation according to claim 18, wherein said active ingredient contains ipratropium bromide and aldbuterol sulfate.
[Claim 21]How to uniform the aerosol pharmaceutical preparation according to claim 17, wherein said propellant contains a hydronaliumfluorocarbon propellant.
[Claim 22]How to uniform the aerosol pharmaceutical preparation according to claim 20, wherein said hydronaliumfluorocarbon propellant is chosen from a group which consists of 1, 1,

1, 2, 3, 3, and 3-heptafluoro propane, tetrafluoro ethane, and those mixtures.
[Claim 23]Said aerosol pharmaceutical preparation Isopropyl myristate of less than about 3weight % of quantity, Acetylation monoglyceride, perfluoro-carboxylic acid, a polyethylene glycol, How to uniform the aerosol pharmaceutical preparation according to claim 17 by which a surface-active agent chosen from a group which consists of a polyethylene oxide sorbitan fatty acid ester, a polyvinyl pyrrolidone, propylene glycol, and oleic acid being included further.
[Claim 24]How to uniform the aerosol pharmaceutical preparation according to claim 13 including further a process of carrying out the bit of said uniformed aerosol pharmaceutical preparation into an aerosol can.
[Claim 25]Equipment which uniforms aerosol pharmaceutical preparation with a closed continuation loop device under a high pressure, comprising:
A means for performing; high voltage uniformity with a mixing vessel; said reaction vessel.
A means for connecting said means for performing high voltage uniformity within a closed continuation loop device.;

[Claim 26]Equipment which uniforms the aerosol pharmaceutical preparation according to claim 24, wherein said means for performing high voltage uniformity maintains a pressure of about 137,895 kilopascals (20,000 psi) to said aerosol pharmaceutical preparation.
[Claim 27]Equipment which uniforms the aerosol pharmaceutical preparation according to claim 24, comprising:
A bypass loop for providing a channel for a pump means for circulating aerosol pharmaceutical preparation in said equipment and the; aforementioned aerosol pharmaceutical preparation to circulate; a bit means and; entrance check valve for carrying out the bit of said aerosol pharmaceutical preparation.
An exit check valve.
A channel for said aerosol pharmaceutical preparation to circulate [have a pneumatic pressure bypass valve further, when said entrance check valve and said exit check valve are closed open said pneumatic pressure bypass valve, and] in said equipment.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]Generally, this invention relates to the method and equipment which uniform the aerosol pharmaceutical preparation which contains a low-boiling point propellant especially about the method and equipment which uniform volatile matter and the mixture containing low boiling material. This invention relates to the method and equipment of superfines-izing the particles of the active substance in aerosol pharmaceutical preparation, and uniforming the pharmaceutical preparation which are both made further.
[0002]
[Description of the Prior Art]An aerosol is a gaseous suspended solid of a detailed particle or liquid particles. Aerosol pharmaceutical preparation is also a gaseous suspended solid containing the solvent or suspended solid of an active ingredient which became a liquid, and this active ingredient consists of a propellant, required arbitrary solvents, an excipient, or a surface-active agent. Generally, a propellant is a low-boiling point liquid which volatilizes under temperature and the ambient conditions of a pressure. In a container, pharmaceutical preparation is held under a pressure, is released from a container through a valve, and forms aerosol spraying. It is designed so that many a substance, for example, drugs, insecticides, and paints may be dramatically supplied with the form of aerosol spraying. Although this invention is generally applicable to preparation of aerosol pharmaceutical preparation, especially this invention is applicable to dispensing of the aerosol pharmaceutical preparation of the drugs meant so that a medicine might be prescribed for the patient by inhalation using the bit equipment called the inhaler (MDI) of the dose supplied while measuring.
[0003]In order to supply spraying of the aerosol of a single composition thing, aerosol pharmaceutical preparation should be homogeneous in the ability to do. About the aerosol pharmaceutical preparation which contains a solid as an active ingredient, it dissociates eventually and the active ingredient should form the suspended solid uniformly distributed with a propellant and other components of the drug product, for example, a solvent, or a surface-active agent. It is required for aerosol pharmaceutical preparation to receive uniformity of a certain kind generally, in this way, before carrying out container stuffing. Since aerosol pharmaceutical preparation contains the propellant which becomes a gas by a usual temperature and pressure (about 20degreeC and 1,013 hPa (1 atmosphere)), uniformity of aerosol pharmaceutical preparation may include a problem. In order to avoid volatilization-ization, aerosol pharmaceutical preparation must be dealt with with either of the temperature which is below a high pressure or the boiling point of aerosol pharmaceutical preparation.
[0004]The homogenizer ordinarily used according to the present way for uniformity of aerosol pharmaceutical preparation is provided with a stowage container and the propeller-like rotor which promotes to a stator the liquid accommodated in the container, and makes a liquid uniform. The homogenizer (a rotor / stator type homogenizer) which can be used now [of this design] does not act to the contents of the stowage container by a high pressure substantially. That is, the homogenizer of a rotor / stator type design can operate only by ambient pressure or a slightly high pressure, and this homogenizer cannot operate by sufficient high pressure to maintain a volatile material at that liquid state. In this way, if a process is carried out at the temperature below the boiling point of a propellant, it can use only for a rotor / stator type homogenizer uniforming the mixture containing a low-boiling-point volatile propellant. When it

does not desire this, when this is impossible, it must appeal to other means as temperature with a low ingredient of aerosol pharmaceutical preparation like [when not being fully miscibility]. In such a situation, the non-volatile output concentrate which consists of an active ingredient and a liquid comparatively comparatively non-volatile with a high boiling point is manufactured in the first place. Since the output concentrate is comparatively non-volatile, this output concentrate can be uniformed using a rotor / stator type homogenizer by ambient air temperature and a pressure. Once it is uniformed, an output concentrate will be mixed with a propellant under a pressure, and will form homogeneous aerosol pharmaceutical preparation.

[0005]in this way -- as a propellant -- CFC12 (CCl_2F_2.) T_b/**C=-29.8 or CFC114 ($C_2Cl_2F_4$.) Inhalation aerosol pharmaceutical preparation of the drugs which contain low-boiling point chlorofluorocarbon (CFC) comparatively like T_b/**C=3.8, it is, for example like [as the activator agent as a solid eventually divided into the 1st] CFC11 (CCl_3F, T_b/**C=23.75) -- with CFC of a high boiling point comparatively. it is known in medicine manufacture technology that it can make by preparing the output concentrate containing a surface-active agent or suspension (for example, a soybean lecithin, oleic acid, and the span (Span) (registered trademark) -- in addition). This output concentrate can be uniformed by ambient air temperature and a pressure using a rotor / stator type homogenizer. Once it is uniformed, an output concentrate and a comparatively low-boiling-point CFC propellant will be introduced into a pressure vessel, and they will form the homogeneous pharmaceutical preparation which was mixed in this container and completed. Subsequently, bit equipment like the equipment of MDI which operates with either a high pressure and ambient air temperature or a low (filled up with a container, ranking second and attaching a lid) temperature and ambient pressure (the retrofilling is carried out through the valve of a container with a lid) is filled up with the completed pharmaceutical preparation.

[0006]In the pharmaceutical preparation mentioned above, CFC of a high boiling point is comparatively useful for three important and peculiar functions. CFC of a high boiling point serves [1st] as a solvent of suspension like a soybean lecithin. In order to secure an exact and reproducible dose, it is required for suspension to be able to dissolve thoroughly into an output (it is only CFC in which high boiling point CFC exists) concentrate, and (both high boiling point CFC and low-boiling point CFC exist) the whole pharmaceutical preparation. High boiling point CFC serves as quality of carrier fluid about the interaction of high boiling point CFC which has [2nd] solid drugs particles. High boiling point CFC serves as a cause of the carburetion pressure the whole last pharmaceutical preparation power the 3rd. The pressures of pharmaceutical preparation are one of the variables which influences optimization of the active-ingredient adhesion in a patient's lung, therefore the effect of pharmaceutical preparation. Since it is a result of contribution of the partial pressure of all CFCs by which the last carburetion pressure power of pharmaceutical preparation is used for pharmaceutical preparation in relation to this, high boiling point CFC is comparatively called a propellant.

[0007]

[Problem to be solved by the invention]The concerns of the latest environment about use of a CFC propellant resulted in substitution of a hydronaliumfluorocarbon alkane (HFA) propellant instead of traditional CFC. It turned out that it cannot use for the method of having mentioned above which prepares the aerosol pharmaceutical preparation which attains uniformity using a rotor / stator type homogenizer by ambient air temperature and a pressure generally making the pharmaceutical preparation which used HFA as the base. There is no permissible high boiling point HFA in particular that can be used for making a non-volatile output concentrate so that it

may be carried out in the case of the CFC pharmaceutical preparation using CFC11 mentioned above. Therefore, low-boiling point HFA, an activator agent, a surface-active agent, and the homogeneous mixture of other components of the drug product must be made. It is clear that it is a high pressure or uniformity of the pharmaceutical preparation containing low-boiling point HFA must be performed at a low temperature. Otherwise, it is because low-boiling point HFA evaporates. However, since the surface-active agent of a large number which do not cause HFA and a chemical reaction cannot dissolve in HFA pharmaceutical preparation at a low temperature, uniforming at a low temperature is not necessarily possible. Therefore, uniformity must be performed at a high temperature.

[0008]A misfortune is used, and as mentioned above, the rotor / stator type homogenizer which operates under sufficient pressure to prevent volatilization of low boiling point components like a propellant do not exist now. Therefore, the existing technology cannot be used for uniforming the pharmaceutical preparation containing low boiling point components like a HFA propellant with ambient air temperature. As further background, when the particle of an active substance should make it become muddy in aerosol pharmaceutical preparation, such particles are dramatically small and he should understand that it must have uniform particle diameter substantially. That is, in order to form a homogeneous suspended solid, the particles of an active ingredient must be superfines-ized. Such superfines-ization is attained by the grinding work usually done before mixing an active substance to pharmaceutical preparation. Since they are in the tendency which generates **** of the active substance showing expensive waste of activity material, manage still more difficult by polluting a production environment by **** of this active substance and cause a worker's risk of happening, such grinding work is not desirable. Since it is wished, however conventional technology does not provide the method or equipment which can be superfines-ized, for example after mixing a solid active substance to aerosol pharmaceutical preparation between uniformity stages as a result, the conventional grinding may be avoided.

[0009]

[Means for solving problem]According to the purpose and other purposes of becoming clear succeedingly which were mentioned above, this invention is dispatched to closed equipment which uniforms aerosol pharmaceutical preparation which has the following elements and which can be pressurized.

(1) A mixing vessel which has an inlet means and an outlet means and which can be pressurized;

(2) It has a homogenizer arranged by carrying out fluid communicating to a reaction vessel, Said homogenizer is provided with two or more nozzles which have a long and slender orifice which ejects a sheet under a pressure of a liquid which should be uniformed, Said nozzle is arranged so that a turbulent flow jet interaction of said sheet may be made to perform along with anterior part of a common jet interaction, Said sheet is ejected by said nozzle along with anterior part of a common liquid ejection interaction in a low pressure zone region filled with said liquid of said sheet, and said sheet, A common boundary constituted and formed with said sheet intrinsically ejected in said said mixture of the area within a low pressure zone and said low pressure zone region is met, A turbulent flow jet interaction in said low pressure zone region filled with said liquid caused further by said nozzle. A means to constitute a jet interaction room constituted so that said low pressure zone region of said liquid organization which is ejected and makes the; aforementioned turbulent flow jet interaction perform might be provided, and a means to eject said liquid organization under; pressure for said nozzle;

(3) It returns from [from said exit of said mixing vessel to a homogenizer] a homogenizer to the

entrance of a mixing vessel, and has a fluid lead pipe which forms closed equipment among them.
[0010]This invention is provided with the following.
The process as which it is sent to how to uniform the aerosol pharmaceutical preparation in a closed continuation loop device under a high pressure, and this method determines the level of a request of uniformity.
The process of mixing the aerosol pharmaceutical preparation in a mixing vessel.
The process which circulates the aerosol pharmaceutical preparation mixed with the high voltage homogenizer.
The process which operates a high voltage homogenizer by sufficient pressure to attain uniformity of the mixed aerosol pharmaceutical preparation, the process which is made to circulate through aerosol pharmaceutical preparation and is returned into a mixing vessel, and the process of repeating the above-mentioned process until it attains uniformity of a predetermined level.
A closed continuation loop device is good to connect with the high voltage filling station filled up with aerosol pharmaceutical preparation by connecting mechanism and a duct means. In the embodiment of a modification, when diluting aerosol pharmaceutical preparation with an aerosol propellant to the aerosol pharmaceutical preparation of predetermined volume, a closed continuation loop device is good to use for preparing the condensed aerosol pharmaceutical preparation which is transported to a large container by a connecting mechanism nozzle conduit means.
[0011]
[Objects of the Invention]Therefore, the purpose of this invention is to provide the improved method and equipment which uniform a volatile mixture. The further purpose of this invention is ambient air temperature, and there is in providing the method and equipment which uniform a volatile mixture, for example, the aerosol pharmaceutical preparation containing a low-boiling point HFA propellant. In addition, supposing the further purpose is processed at a low temperature of this invention, there is in providing the method and equipment which enable preparation of aerosol pharmaceutical preparation which has a wide range surface-active agent containing the surface-active agent which cannot be mixed with dispensing. The purpose of further others of this invention provides the method and equipment of superfines-izing the particles of the active substance in aerosol pharmaceutical preparation, and uniforming aerosol pharmaceutical preparation which are both made, and there is in removing the demand of the conventional pulverizing of an active substance.
[0012]Other purposes of this invention will become clear still more easily, when they consider detailed explanation of the following of the desirable embodiment of this invention about an accompanying drawing. The structure of this invention, an operation, and an advantage will become clear when they take into consideration non-limiting explanation of the following of some embodiments of this invention about an accompanying drawing.
[0013]
[Mode for carrying out the invention]Reference of drawing 1 will show a 1st embodiment of the equipment of this invention. Generally, the equipment of this invention is provided with the connector 30 (a) which connects the component parts of the mixing means 40 with the lead pipes 31, 32, 33, and 34, and 30 (b) in order to form the mixing vessel 10 provided with the mixing means 40, the high voltage homogenizer 12, and a closed continuation loop device. Once it is sealed, the whole equipment can process with equipment the aerosol pharmaceutical preparation

which operates under a pressure and contains a volatile propellant with ambient air temperature. The mixing vessel 10 is constituted so that aerosol pharmaceutical preparation may be accommodated, and it has a crowning (not shown) with which a mixing vessel is made to load and which can be removed. As for the mixing vessel 10, it is good that it is a 3785 cubic centimeters (1 gallon) stirring type floor lamp reactor of the pearl (Parr) model 4550 for example.

[0014]The high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain instantaneous superfines-ization of the particle in aerosol pharmaceutical preparation, when it can apply with uniformity and is wanted. As for the high voltage homogenizer 12, it is good that it is micro fluidics (Microfluidics) model M-110F Micro fluidizer (Microfluidizer) (registered trademark) for example. The equipment and the operating method of a Micro fluidizer (registered trademark), It is explained to US,4,908,154,B published in Cook (Cook) etc. on US,4,533,254,B published in Cook (Cook) etc. on August 6, 1985, and March 13, 1990 still in detail, and they are used here. The brief explanation of an operation of the homogenizer 12 is as follows. The homogenizer 12 has the entrance 13 connected with the high pressure pumping 15 with the lead pipe 32, has the pressure surveillance gauge 17 attached to the exit pipe 33, and propels material under a pressure by the jet interaction room block means 18. The fixed procedure of grinding of particles, distribution, and uniformity happens in the interaction interior of a room. Three different power which attains a required result, i.e., shearing, impaction, and a cavitation are used for the jet interaction room block means 18.

[0015]If a fluid flow is promoted into the interaction room 18 with high voltage, a fluid flow will go into the interaction room entrance 19, and will be divided into the two laminar flow 22 and 23 by the flow splitter 20. Each flow goes into the channel (not shown) of a jet interaction room block. A channel is formed by machining a slot into two blocks which faced each other and fitted in exactly. Shearing force is applied to the fluid flow in alignment with the wall of a channel. A channel pulls apart each laminar flow mutually, and it ranks second, and it is constituted so that it may draw near mutually. The flows 22 and 23 gather in the impaction room 28, and collide mutually with high voltage in the space which has comparatively larger cross sectional area and volume than the cross sectional area and volume of two channels. A fluid flow is made to produce a cavitation by this rapid change of a cross sectional area and volume. Moreover, two flows produce impaction from it being [being high voltage and] high-speed, and colliding mutually. The produced flow is uniformed and any particles in pharmaceutical preparation are superfines-ized. The produced flow leaves the interaction room 18 from the interaction room exit 29, and is returned to the mixing vessel 10 via the connector 14 with the lead pipe 34.

[0016]The homogenizer which has the structure mentioned above superfines-izes the organic drugs compound suspended into the liquid. The grade of uniformity, i.e., reduction of particle diameter, is controllable by the length of the time which circulates the inside of equipment [fluid flow / containing the size and the particle of the energy input from the pump 15, and the channels 22 and 23]. Other factors which determine the effect of processing have the peculiar character, for example, the hardness, the viscosity, others, and the relation of a specific material processed. The component parts of closed equipment are connected by the connector 30 (a) and 30 (b), and these connectors suit the pressure of equipment, and the ingredient and chemical reaction of aerosol pharmaceutical preparation are not caused. As for the connector 30 (a) and 30 (b), it is good that they are stainless steel, a plastic, or a rubber tube for example. The connector 30 (a) and each of 30 (b) are good optionally to finish with "rapid connection" coupling, and, as a result, can carry out an assembly and decomposition for equipment easily.

[0017]The connector 30 (a) and 30 (b) serve as a means to connect a lead pipe with the element of equipment. An active ingredient and a required surface-active agent, or other components of the drug product are added to the mixing vessel 10 except for a volatile component during use. Typically, the mixing vessel 10 has a lid (not shown) which can remove [that sealing which can be removed in order to introduce these components of the drug product into a container with a sufficient condition is possible, and]. Once these non-volatile ingredients are introduced, the mixing vessel 10 will be sealed. An active ingredient is good to include an effective quantity pharmaceutically [the respiratory compound of activity] pharmaceutically for example. An active ingredient contains ipratropium bromide and the aldbuterol sulfate (albuterol sulfate), for example. An active ingredient may be a superfines-ized form or may be a form which has not been superfines-ized.

[0018]A possible surface-active agent Acetylation monoglyceride like the isopropyl myristate and MIBASETTO (Myvacet (registered trademark)) 9-08 for example, Perfluoro-carboxylic acid (perfluorocarboxylic acid), A polyethylene glycol (PEG200, 300 and 400, or 600), A polyethylene oxide sorbitan fatty acid ester (Tween (Tween (registered trademark)) 20, 40, 60, 65, and 80 or 85), Sorbitan ester, such as sorbitan monolaurate, sorbitan monooleate, and sorbitan palmitate, a polyvinyl pyrrolidone (K17;K25;K30 or K90), propylene glycol, and oleic acid are included. A surface-active agent is good to add 0.1 to 0.5weight % of quantity, or more based on the gross weight of a constituent. The total amount of the surface-active agent should be less than about 3 weight %.

[0019]When aerosol pharmaceutical preparation is sensitive to moisture and air, before putting aerosol pharmaceutical preparation into a mixing vessel, it is necessary to purge equipment with super-high-purity nitrogen. A propellant is supplied to the reaction vessel 10 under a pressure from the entrance 11 with a valve. A propellant, for example Low boiling point hydrocarbon (1, 1, 1, 2, 3, 3, and 3-heptafluoro propane), i.e., HFA-227, It is good that they are HFA-134a (tetrafluoro ethane) or HFA-227 and a HFA propellant like the compound of HFA-134a, CFC12, CFC propellants like 114, or those mixtures. A propellant is good to include a solvent, for example, alcohol like ethanol. Although an output concentrate can be made, according to environment, it is not necessary from the process of this invention to make. When working in batch (about 3 l. of pharmaceutical preparation) of a small laboratory scale, it is in good order to uniform directly the components of the drug product which have the quantity of sufficient propellant to jump over the process of making an output concentrate and make perfect pharmaceutical preparation. (For example, 3 l. is exceeded) About a large-scale batch, it is preferred to make a homogeneous output concentrate, to rank second and to dilute it with an additional propellant suitably.

[0020]If all the ingredients of aerosol pharmaceutical preparation are once in the mixing vessel 10 and a mixing vessel is pressurized by 552 kilopascals (from 70 psi to 80 psi) from about 483 kilopascals, aerosol pharmaceutical preparation will be ready for mixing, uniformity, and superfines-izing. Mixing is attained by the agitating equipment 40 arranged in the mixing vessel 10. As for the agitating equipment 40, being set as speed of about 400 rpm is preferred. While the contents of the mixing vessel are once stirred completely and agitating equipment is still operating,; pharmaceutical preparation which opens the outlet valve 50 and is made to circulate pharmaceutical preparation through the inside of equipment in following order, It flows from the mixing vessel 10 in the valve 50, the connector 30 (b), and the homogenizer 12, and it ranks second and returns from the connector 30 (a) to the mixing vessel 10. The mixing vessel 10 is optionally provided with the drain 51 which makes easy washing of a mixing vessel, or removal

of the remaining output.
[0021]Pharmaceutical preparation is ipratropium bromide (it superfines-ized). 45.0 g Isopropyl myristate It is good to include 75.0 g 1, 1, 1, 2, 3, 3, and 3-heptafluoro propane 74.88-kg*.
* During restoration, this quantity contains the surplus amount of the propellant introduced while processing in order to compensate the steam which remains in the sealed manufacture tank, when decreasing a liquid increase-in-quantity suspended solid. It is good to add super-high-purity nitrogen to the mixing vessel 10 from the valve 9, and to bring a reaction vessel pressure up to about 689 kilopascals (100 psi). This superfluous pressure assists circulation of the aerosol pharmaceutical preparation in equipment.
[0022]When the active ingredient used as a starting material is a liquid or the already superfines-ized solid, the high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain uniformity of aerosol pharmaceutical preparation. When the active ingredient used as a starting material is a solid which is not superfines-ized, the high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain instantaneous superfines-izing and uniformity of aerosol pharmaceutical preparation. The part depends on active-ingredient itself for the pressure used for uniformity, superfines[instantaneous]-izing, and uniformity. A certain active ingredient may take a still higher pressure and still longer processing time to attain the result of a request with the peculiar character of those crystal structures.
[0023]For example, when the superfines-ized active ingredient is used as a starting material, typically, the high voltage homogenizer 12 is set up supply the pressure of about 55,158 to 62,053 kilopascals (from 8,000 psi to 9,000 psi) to aerosol pharmaceutical preparation. Supposing the active ingredient which is not superfines-ized is used as a starting material as a modification, typically, the means 12 for high voltage uniformity and superfines-izing will be set up give the pressure of about 137,895 kilopascals (20,000 psi) to aerosol pharmaceutical preparation. aerosol pharmaceutical preparation -- the level of a request of uniformity -- applicable -- if it becomes, it will circulate until the level of a request of superfines-izing is attained. Typically, this needs the passage of at least ten volume exchange in equipment.
[0024]It is good during the operation of the high voltage homogenizer 12 to have the means 60 for cooling the high voltage homogenizer 12. As for this means 60, it is good that they are an ice bath or a refrigeration unit for example. This is performed in order to prevent accumulation of the superfluous heat produced from the impaction of high-speed particles and particles produced within the high voltage homogenizer 12. By the cooling method 60, in order to maintain a pressure below to about 1,034 kilopascals (150 psi), the temperature and the pressure of the high voltage homogenizer 12 are reduced. According to one embodiment, by the cooling method 60, while a high voltage homogenizer and the micronizer 12 are in use, the pressure to about 16degreeC is reduced for the temperature of a homogenizer up to about 586 kilopascals (85 psi). When the process of uniformity or instantaneous superfines-izing, and uniformity is completed, as for aerosol pharmaceutical preparation, preparation of a bit process is completed. The bit of the completed aerosol pharmaceutical preparation is carried out into a container by two different methods. When the completed pharmaceutical preparation is not injured by cold, pharmaceutical preparation is cooled below at that boiling point, it ranks second, and while being taken out from the application-of-pressure homogenizer of this invention works at a good and still low temperature, the open container is filled up, it ranks second and a lid is attached to this container. Drawing from the pressurizer of this invention is performed by connecting the exit of the mixing vessel 10 with a suitable dispenser, using ordinary technology, the known small amount of an

aerosol composition is sent out to an aerosol can, a lid is attached to this aerosol can, and this dispenser is sealed.
[0025]When producing as a modification reduction of the quantity of the surface-active agent which can dissolve in pharmaceutical preparation by cooling of pharmaceutical preparation, restoration of a container must be performed by ambient air temperature and a high pressure using closed equipment. Other embodiments of this invention explained below function this latter. Reference of drawing 2 will show a 2nd embodiment of this invention. Although this is the same as that of a 1st embodiment, it has an additional means for operating under a high pressure by uniforming, carrying out the bit of the superfines-ized aerosol pharmaceutical preparation into the container sealed by the Klin ping, supposing it is applicable, and carrying out the retrofilling from the valve of a container with a lid simultaneously. A common reference number is applied to the same items, and as mentioned above, it operates. For example, if drawing 2 is continued and referred to, as mentioned above, it will add to the mixing vessel 10, the high voltage homogenizer 12, the connector 30 (a), and 30 (b), Equipment is further provided with the three way valve 100, the pump 70, other three way valves 101, the by-pass line loop 110, the entrance check valve 120, the dispenser 80, the exit check valve 130, and the pneumatic pressure bypass valve 90. Optionally, equipment is good to have further the serial flow instruments 170 and 171 which supervise the flow of pharmaceutical preparation through the whole processing loop.
[0026]The pump 70 constitutes the means for circulating aerosol pharmaceutical preparation in equipment among the operating time of equipment, when pharmaceutical preparation separates and is shunted from a homogenizer and the micronizer 12. As for the pump 70, it is good that it is micropump (Micropump) (registered trademark) model 152-000 magnetic pumping for example. The by-pass line loop 110 provides the channel which circulates aerosol pharmaceutical preparation, when aerosol pharmaceutical preparation is not turned to the dispenser 80. The by-pass line loop 110 is good to be made by the inactive plastic or the tube of rubber by a stainless steel tube or the material processed. The dispenser 80 is a means for carrying out the bit of the aerosol pharmaceutical preparation into an aerosol can. As for the dispenser 80, it is good that they are PAMAZORU (Pamasol)(registered trademark) 2016 / 1 pressure filling machine for example.
[0027]The serial flow instrument 170 is good to be arranged just behind the three way valve 100, and to arrange other serial flow instruments 171 just before the reaction vessel 10. The operation of the equipment provided by 2nd embodiment of this invention except for a transfer of the pharmaceutical preparation into the container sealed by the Klin ping processed thoroughly is the same as that of a 1st embodiment. That is, supposing equipment is loaded with an active ingredient, a propellant, and other components of the drug product, pharmaceutical preparation is uniformed by the same method as having mentioned above with reference to a 1st embodiment and it is applied, a solid active ingredient will be superfines-ized. The equipment provided by 2nd embodiment separates the pharmaceutical preparation processed thoroughly from the homogenizer 12, and it differs from a 1st embodiment in that it has an added component made to be turned to the direction of the dispenser 80 a container can be filled up with pharmaceutical preparation.
[0028]While carrying out the process of uniformity or instantaneous superfines-izing, and uniformity, :pharmaceutical preparation which flows in the element of the embodiment shown in drawing 2 in order of the following [pharmaceutical preparation / aerosol] leaves the mixing vessel 10, The drain valve 50, the lead pipe 30 (c), the three way valve 100, the lead pipe 30 (d), the high voltage homogenizer 12, the lead pipe 30 (e), It flows in the three way valve 101, the

lead pipe 30 (f), the optional flow instrument 170, lead pipe 30(i), the bypass connector 110, the open bypass valve 90, the lead pipe 30 (n), the optional flow instrument 171, and the lead pipe 30 (o), and it ranks second and returns into the mixing vessel 10. once -- uniformity -- applicable -- if it becomes and superfines-ization will be completed, the flow of pharmaceutical preparation will be diverted from the homogenizer 12 to the pump 70 by the operation of the three way valves 100 and 101 with the lead pipe 30 (g) and the lead pipe 30 (h). The high voltage homogenizer 12 is removed from the circulation flow passage of aerosol pharmaceutical preparation, in order to avoid superfluous processing of aerosol pharmaceutical preparation. As for this time, the pump of the high voltage homogenizer 12 caused circulation of the pharmaceutical preparation in equipment. Once the flow of pharmaceutical preparation is diverted from the high voltage homogenizer 12, the pump 70 will take over this work. Like the agitating equipment 40 of the reaction vessel 10, the pump 70 does sufficient stirring so that a suspended solid may be maintained. When both the temperature after circulation with the pump 70 for about 15 minutes and in a container and a pressure increase to the value near those first values, it is good for a bit to start.

[0029]The bit of pharmaceutical preparation is controlled by concurrent operation of the two check valves 120 and 130 and the pneumatic pressure bypass valve 90. It is filled up with the pharmaceutical preparation of the volume which opened the entrance check valve 120 and the exit check valve 130, set up the pneumatic pressure bypass valve 90 close the bypass 110, circulated the inside of the lead pipe 30 (j) and the valve 120, and was beforehand set as the dispenser 80 in pharmaceutical preparation by that cause in order to begin a bit process. Once it fills up, excessive pharmaceutical preparation will leave the dispenser 80 and will flow backwards to a reaction vessel through the lead pipe 30 (q), the open check valve 130, the lead pipe 30 (m), the bypass valve 90, the lead pipe 30 (n), the optional flow instrument 171, and the lead pipe 30 (o). The aerosol can which a lid is attached and has a suitable valve is filled up with aerosol pharmaceutical preparation. The valve of the container with which it should be filled up is pressed fit and liquid free passage connection is carried out with the port 85 with a valve of the dispenser 80. Thereby, the pharmaceutical preparation of the volume in the dispenser 80 set up beforehand is made to blow off from the dispenser 80, and the retrofilling is carried out through the valve of a container.

[0030]When pressing the valve of a container fit and carrying out liquid free passage connection with the port 85 of the dispenser 80, it closes automatically, the pneumatic pressure bypass valve 90 is reset automatically, and the entrance check valve 120 and the exit check valve 130 enable passage in the bypass 110 of pharmaceutical preparation. In this way, the flow of pharmaceutical preparation is detached and diverted from the dispenser 80, and the flow of pharmaceutical preparation fills a container simultaneously. By demounting the filled container from liquid free passage connection in the port 85 of the dispenser 80, the two check valves 120 and 130 are opened automatically, close the pneumatic pressure bypass valve 90 simultaneously, and enable pharmaceutical preparation to flow in the dispenser 80. The dispenser 80 is re-loaded with the pharmaceutical preparation of the quantity set up beforehand by this, and the preparation filled up with other containers is completed in the dispenser 80.

[0031]Drawing 3 and especially drawing 4 illustrate simultaneously other embodiments of this invention applicable to production of the large batch of aerosol pharmaceutical preparation, i.e., the batch of an industrial scale. A common reference number is applied to the same items, and as mentioned above, it operates. For example, the mixing vessel 10 and the; drain valve 50 in which manufacture of the batch of an industrial scale and the equipment of this invention which carries

out a bit have the mixed adjustable vane 40, and the; lead pipe 30 (a) and; high voltage homogenizer 12; it has the additional lead pipe 30 (b),; return-line coupler 160, and; return-line valve 150. As shown in drawing 4, the pharmaceutical preparation container 140 holds aerosol pharmaceutical preparation for a bit process. As for the pharmaceutical preparation container 140, it is good that it is a well-closed container of stainless steel for example. The return-line coupler 160 is a means for connecting the end of the lead pipe 30 (b) with either the reaction vessel (as [show / in drawing 3]) 10, or (as [show / in drawing 4]) the pharmaceutical preparation container 140. For example this coupler 160 constitutes what is called a rapid connection coupler of a lot, and is used for a male coupler making the lead pipe 30 (b) finish, and the corresponding female coupler in which doubling is possible exists as a port to the containers 10 and 140.

[0032]Like [in case connection is switched to another side from one side], the return-line valve 150 constitutes the means for closing the flow of pharmaceutical preparation, when the lead pipe 30 (b) is connected with the container 10 or neither of 140. Since what is called a rapid connection coupler has a valve of one closed automatically when two half parts of coupling are separated, it is [the return-line valve 150] in good order to be contained as an integral part of the connecting mechanism 160. It is good to carry out using the embodiment of the invention which are uniformity of aerosol pharmaceutical preparation, and the method substantially same supposing it is applicable as the embodiment which shows drawing 1 superfines-ization, and is shown by drawing 3 and drawing 4. That is, the reaction vessel 10 is filled with the non-volatile ingredient which must be in the active ingredient (this active ingredient may be superfines-ized or it is not necessary to superfines-ize it if it is a solid) of desired quantity, arbitrary surface-active agents, a solvent, or pharmaceutical preparation. Subsequently, a container is sealed and a propellant is introduced under a pressure from the port 11 with a valve. However, it is preferred to introduce a quantity smaller than all the quantity of the propellant needed for constituting the completed pharmaceutical preparation in the case of large batch, i.e., batch of an industrial scale. In this way, it is preferred to make an output concentrate first and this output concentrate can be processed with the homogenizer 12 still more easily than the completed pharmaceutical preparation which contains all the quantity of a propellant according to that volume not being comparatively large. Superfines-ization is performed by uniformity and the equipment constituted as it was shown in drawing 3, supposing it was applicable, and this equipment is functionally [as the equipment shown by drawing 1] equivalent. The operation of the equipment constituted as shown in drawing 3 is the same as that of the embodiment shown in drawing 1.

[0033]For a bit process, the drain valve 50 of the reaction vessel 10 is bolted to the high voltage homogenizer 12. Subsequently, the aerosol pharmaceutical preparation which was superfines-ized and was uniformed is made to transport to the pharmaceutical preparation container 140 by the procedure of explaining below. The return-line valve 150 between the high voltage homogenizer 12 and a reaction vessel is closed. The high voltage homogenizer 12 is terminated. All aerosol pharmaceutical preparation should be in the reaction vessel 10. As for the return-line coupler 160, engagement is canceled of the reaction vessel 10. Reference of drawing 4 will connect the return-line coupler 160 with the pharmaceutical preparation container 140. The drain valve 50 is made to lead to the high voltage homogenizer 12, and high-pressure uniformity and superfines-izing are started. Aerosol pharmaceutical preparation is transported to the pharmaceutical preparation container 140 by a high pressure from the reaction vessel 10. The agitating equipment 180 of the pharmaceutical preparation container 140 is made to start. When almost all aerosol pharmaceutical preparation is transported, the drain valve 50 of the reaction

vessel 10 is closed, and the high voltage uniformity unit 12 is terminated.
[0034]As for the procedure of a rinse, it is preferred that it is as follows. The propellant (in the case of a 3.8L mixing vessel, 3 l. or less is preferred) of a certain quantity for rinsing the mixing vessel 10 is added to the mixing vessel 10. The volume for [of a propellant / this] rinsing is preferably stirred in about 5 minutes and within the container 10. The drain valve 50 of the mixing vessel 10 is made to lead to the high voltage homogenizer 12, and the high voltage homogenizer 12 is made to start. The high voltage homogenizer 12 feeds the volume which a propellant rinses in the pharmaceutical preparation container 140. It is preferred to cause much more many of these procedures of several times to rinse. It is preferred to use at least 4 times of the procedures to rinse. When a rinse is completed, by the inlet port 141 with a valve, the remaining quantity of the propellant which takes aerosol pharmaceutical preparation to bring to the last aerosol pharmaceutical preparation is made to act under a pressure, and is quantitatively applied to the pharmaceutical preparation container 140. The agitating equipment 180 of the pharmaceutical preparation container 140 continues operating.
[0035]And it is good to fill up each container using the technology which mentioned above the aerosol pharmaceutical preparation in a pharmaceutical preparation container. That is, it is ambient air temperature, and while acting at the temperature below the boiling point of a propellant and the pharmaceutical preparation which carried out the bit, it is good to transport pharmaceutical preparation to an open container from the container 140, to rank second and to seal this open container using a lid and a valve assembly. As a modification, while acting by ambient air temperature and a high pressure, it is good to fill up a container with a lid with the pharmaceutical preparation in the container 140 using a dispenser like the means 80 built into the embodiment shown in drawing 2. Various aerosol pharmaceutical preparation was made using the manufacturing process of the batch of this industrial scale. For example, the aerosol pharmaceutical preparation of ipratropium bromide / HFC-227, and aldbuterol sulfate / HFC-227 were manufactured using the process of this invention. In addition, the ipratropium bromide / HFC-227 using the active ingredient which has not been superfines-ized were manufactured using the process of this invention.
[0036]
[Working example]According to the following working examples, the desirable embodiment of this invention within the limits is described further, and is proved. Although these working examples belong to the aerosol pharmaceutical preparation for medical application, this invention is suitable also for application of other industries, for example, a paint, cosmetics, and a deodorant. Since it is possible to carry out many modification of this invention, without deviating from the pneuma and the range of this invention, these working examples are given for the purpose of illustration, and should not be interpreted as what limits this invention.
(Working-example 1-4) The working example 4 shows the MDI pharmaceutical preparation which prepared the superfines-ized active ingredient from the ingredient of the following used as a starting material with reference to drawing 2 from the following working examples 1, using the method and equipment of this invention.
[0037]
[Table 1]Table 1. ----------. Working example Active ingredient Surface-active agent Propellant. ----------. 1 The superfines-ized --- HFC-227 ipratropium bromide. ----------. 2 It superfines-ized. --- HFC-227 aldbuterol sulfate. ----------. 3 It superfines-ized. Isopropyl HFC-227 ipratropium bromide Millis Tait. ----------. 4 the superfines-ized oleic acid and HFC-227

ipratropium bromide a span -- and -- and -- Superfines-ized isopropyl Aldbuterol sulfate Millis Tait. It added to the reaction vessel 10 with the quantity calculated so that a therapy dose might be given, when positioning a constituent for a ---------- ---------- active ingredient to an aerosol can with a throttle valve, and a required surface-active agent. a surface-active agent -- about 3 or less weight % of an effective dose -- it added. It added to the reaction vessel 10 which sealed the reaction vessel and sealed super-high-purity nitrogen. Super-high-purity nitrogen was added and it came that it was up to 348 kilopascals (50 psi) about the last reaction vessel pressure. With super-high-purity nitrogen, the pressure in the reaction vessel 10 was purged slowly. The purge was stopped when a reaction vessel pressure decreased up to 69 kilopascals (10 psi).

[0038]The propellant was supplied to the reaction vessel 10. Super-high-purity nitrogen was added to the reaction vessel 10, and it came that it was up to 689 kilopascals (100 psi) about a reaction vessel pressure. The agitating equipment 40 of the reaction vessel 10 was started, and it was set as speed of 400 rpm. Stirring was continued for about 15 minutes before the process of continuing. While the agitating equipment 40 was operating at 400 rpm in addition, the drain valve 50 of the reaction vessel 10 was made to lead to the high voltage homogenizer 12. H_2O obtained by a small quantity distilling was placed into the pressure intensifier pump of the high voltage homogenizer 12, in order to carry out the lubrication of the seal. The added water did not have influence harmful to the stability in early stages of pharmaceutical preparation with the water which did not rise [of the manufactured aerosol] notably and was added. The high voltage homogenizer 12 was set up about the homogenizing step supply the pressure of 55158 kilopascals (8000 psi) to aerosol pharmaceutical preparation.

[0039]The inside of the following elements was circulated for aerosol pharmaceutical preparation in an order.

reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(d); high voltage homogenizer 12; -- three way valve 101; besides lead pipe 30 (e); -- lead pipe 30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i); bypass loop 110. or lead pipe 30 (j) and entrance check valve 120, dispenser 80 and exit check valve [either one of] 130; -- a lead pipe -- 30(m); pneumatic pressure bypass valve 90; -- it returns into lead pipe 30 (n); and the reaction vessel 10, and operating agitating equipment was continued within the reaction vessel 10 This was all the circulation flow passages of the aerosol pharmaceutical preparation about a homogenizing step. The whole equipment was bolted to outside environment. Processing frequency of ten volume exchange was carried out. The ice bath was held in the heat exchanger of the parts of a high voltage homogenizer and the micronizer 12 during the operation of the homogenizer 12. By it, vessel temperature decreased to 16degreeC and maintained the pressure to 586 kilopascals (85 psi) during the operation of the high voltage homogenizer 12.

[0040]The bit process is as follows. By diverting the three way valve 100 from the high voltage homogenizer 12 to the pump 70, the high voltage homogenizer 12 was demounted from the circulation flow passage. For the bit process, the inside of the following elements was circulated for aerosol pharmaceutical preparation with the pump 70 in an order.

reaction vessel 10; drain valve 50; -- a lead pipe -- 30. the bypass loop 110 or the entrance check valve 120, the dispenser 80, and the lead pipe 30 (q); (c) --; three way valve 100; -- a lead pipe -- 30(g); pump 70; -- three way valve 101; besides lead pipe 30 (h); -- lead pipe 30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i). either one of [and] the exit check valve 130 or a lead pipe (m) 30 --; pneumatic pressure bypass valve 90; -- it returned into lead pipe 30 (n); and the reaction vessel 10. This was all the circulation flow passages of the aerosol pharmaceutical

preparation which a bit process attaches. Aerosol pharmaceutical preparation was circulated for 15 minutes with the pump 70. Subsequently, the bit of the aerosol pharmaceutical preparation was carried out into the can of MDI. When circulating aerosol pharmaceutical preparation, the container with a valve which carried out crimp has been arranged under the valve port 85 of the dispenser 80. The aerosol pharmaceutical preparation of the volume set up beforehand was supplied to the container. When pushing the valve port 85 on the valve of a container, the entrance check valve 120 and the exit check valve 130 are closed automatically, the pneumatic pressure bypass valve 90 is opened, and the channel for the aerosol pharmaceutical preparation which still circulates through the inside of equipment is provided.

[0041](Working-example 5-8) The working example 8 shows the MDI pharmaceutical preparation which prepared the superfines-ized active ingredient from the ingredient of the following used as a starting material with reference to drawing 2 from the following working examples 5, using the method and equipment of this invention.

[0042]

[Table 2]Table 2. ----------. Working example Active ingredient Surface-active agent Propellant. ----------. 5 --- Freon 12 / 114 ipratropium bromide superfines-ized Mixture. ----------. 6 Superfines-ized soybean Freon 11 and ipratropium bromide Lecithin It reaches Freon 12. Freon 114 mixture. ----------. 7 The --- HFC-227 ipratropium bromide which has not been superfines-ized. ----------. 8 --- HFC-227 which has not been superfines-ized -- the aldbuterol sulfate ---------- ---------- active ingredient and the required surface-active agent were added to the reaction vessel 10. It is preferred about 3 or less weight % of quantity and to add a surface-active agent. It added to the reaction vessel 10 which sealed the reaction vessel and sealed super-high-purity nitrogen. Super-high-purity nitrogen was added and it came that it was up to 348 kilopascals (50 psi) about the last reaction vessel pressure. With super-high-purity nitrogen, the pressure in the reaction vessel 10 was purged slowly. The purge was stopped when a reaction vessel pressure decreased up to 69 kilopascals (10 psi).

[0043]The propellant was supplied to the reaction vessel 10. Super-high-purity nitrogen was added to the reaction vessel 10, and it came that it was up to 689 kilopascals (100 psi) about a reaction vessel pressure. The agitating equipment 40 of the reaction vessel 10 was started, and it was made speed of 400 rpm. Stirring was continued for about 15 minutes before the process of continuing. While the agitating equipment 40 was operating at 400 rpm in addition, the drain valve 50 of the reaction vessel 10 was made to lead to the high voltage homogenizer 12. H_2O obtained by a small quantity distilling was placed into the pressure intensifier pump of the high voltage homogenizer 12, in order to carry out the lubrication of the seal. It did not have influence harmful to the stability in early stages of pharmaceutical preparation with the water which did not rise [of the manufactured aerosol] notably with the added water, and was added. The high voltage homogenizer was set up about superfines-izing and a homogenizing step give the pressure of 137,895 kilopascals (20,000 psi) to aerosol pharmaceutical preparation.

[0044]The inside of the following elements was circulated for aerosol pharmaceutical preparation in an order.

reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(d); high voltage homogenizer 12; -- three way valve 101; besides lead pipe 30 (e); -- lead pipe 30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i); bypass loop 110. exit lead pipe 30 (j) and entrance check valve 120 or dispenser [and] 80, lead pipe 30 (q), or check valve 130 or; -- a lead pipe -- 30(m); pneumatic pressure bypass valve 90; -- it returns into lead pipe 30 (n);

and the reaction vessel 10, and operating agitating equipment was continued within the reaction vessel 10 This was all the circulation flow passages of simultaneous superfines-izing and the aerosol pharmaceutical preparation about a homogenizing step. The whole equipment was bolted to outside environment. The processing time of ten volume exchange was used. The ice bath was held in the heat exchanger of the parts of the high voltage homogenizer 12 during the operation of the homogenizer 12. By it, vessel temperature decreased to 16degreeC and maintained the pressure by 586 kilopascals (85 psi) during the operation of the high voltage homogenizer 12.
[0045]The bit process is as follows. By diverting the three way valve 100 from the high voltage homogenizer 12 to the pump 70, the high voltage homogenizer 12 was demounted from the circulation flow passage. For the bit process, the inside of the following elements was circulated for aerosol pharmaceutical preparation with the pump 70 in an order.
reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(g); pump 70; -- three way valve 101; besides lead pipe 30 (h); -- a lead pipe -- the 30(i); above-mentioned of was done -- as -- the bypass loop 110 or the dispenser 80. Aerosol pharmaceutical preparation was circulated for 15 minutes with the micropump 70. Subsequently, the bit of the aerosol pharmaceutical preparation was carried out into the can of MDI. Using the suitable valve, these containers attached the lid and crimp had already been carried out. When circulating aerosol pharmaceutical preparation, the container with a valve which carried out crimp was arranged under the valve port 85 of the dispenser 80. The aerosol pharmaceutical preparation of the volume set up beforehand was supplied to the container. When pushing the dispenser 80 on the valve of a container, the entrance check valve 120 and the exit check valve 130 are closed automatically, the pneumatic pressure bypass valve 90 is opened, and the channel for the aerosol pharmaceutical preparation which circulates through the inside of equipment in addition is provided.
[0046](Comparative example 4) When the Micro fluidizer (registered trademark) of micro fluidics is used as the high voltage homogenizer and the micronizer 12 for uniformity, The done output had the particle size distribution of the aerosol pharmaceutical preparation prepared using the uniformity method of of ordinary stator / rotor type, and the same particle size distribution. The graphical representation of the mean particle diameter to the processing time of sieve DAIZA about this comparative example is shown in drawing 5. So that drawing 6 which plotted the balancer product particle diameter to the processing time of sieve DAIZA when operating sieve DAIZA by 55,158 kilopascals (8K psi) for uniformity may show, The triangle 6a expresses the CFC output prepared by sieve DAIZA, and the rhombus 6b expresses the CFC output prepared using the rotor / stator type homogenizer. When the already superfines-ized active ingredient is used, particle size distribution does not receive harmful influence with the homogenizer and the micronizer 12 which uniform. Rather, particle size distribution is substantially [as the time of using a rotor / stator type homogenizer] the same.
[0047](Comparative example 5) In order to superfines-ize the active ingredient which has not been superfines-ized, when the Micro fluidizer (registered trademark) of micro fluidics is used as a high voltage homogenizer and the micronizer 12, The particle size of the beginning of an active ingredient is reduced only 30% to the value which is equal to the value obtained about the aerosol pharmaceutical preparation at the time of using the superfines-ized active ingredient as a starting material. The particles which have the size within the limits of 12 (micrometer) to 15 micrometers (micrometer) were manufactured by this method. The graphical representation of the volume particle diameter of the average to the processing time of sieve DAIZA is shown in drawing 5. The round point 5a expresses the output prepared by sieve DAIZA using the active

ingredient which has not been superfines-ized, and the rectangle 5b expresses the CFC output for commerce prepared using the rotor/stator. A particle size is beneficially reduced, when used for the homogenizer 12 uniforming when the active ingredient which has not been superfines-ized is used so that drawing 6 may show. Moreover, a particle size is not influenced by the rotor / stator type homogenizer use for uniformity. Although this invention was explained in relation to the specific embodiment, many modifications and modification should understand that it is clear to a person skilled in the art in the light of the above-mentioned explanation. For example, although the desirable embodiment of this invention is dispatched to the equipment and the method of uniforming the aerosol pharmaceutical preparation which used the HFC propellant, one ingredient may use the equipment and the method of this invention to the volatile mixture which has a low-boiling point. Therefore, this invention plans to include all the things of the modification included in the pneuma of the claim of Claims, and the range, and modification. As a result, reference document referred to on these Descriptions is applied.

TECHNICAL FIELD

[Field of the Invention]Generally, this invention relates to the method and equipment which uniform the aerosol pharmaceutical preparation which contains a low-boiling point propellant especially about the method and equipment which uniform volatile matter and the mixture containing low boiling material. This invention relates to the method and equipment of superfines-izing the particles of the active substance in aerosol pharmaceutical preparation, and uniforming the pharmaceutical preparation which are both made further.

PRIOR ART

[Description of the Prior Art]An aerosol is a gaseous suspended solid of a detailed particle or liquid particles. Aerosol pharmaceutical preparation is also a gaseous suspended solid containing the solvent or suspended solid of an active ingredient which became a liquid, and this active ingredient consists of a propellant, required arbitrary solvents, an excipient, or a surface-active agent. Generally, a propellant is a low-boiling point liquid which volatilizes under temperature and the ambient conditions of a pressure. In a container, pharmaceutical preparation is held under a pressure, is released from a container through a valve, and forms aerosol spraying. It is designed so that many a substance, for example, drugs, insecticides, and paints may be dramatically supplied with the form of aerosol spraying. Although this invention is generally applicable to preparation of aerosol pharmaceutical preparation, especially this invention is applicable to dispensing of the aerosol pharmaceutical preparation of the drugs meant so that a medicine might be prescribed for the patient by inhalation using the bit equipment called the inhaler (MDI) of the dose supplied while measuring.

[0003]In order to supply spraying of the aerosol of a single composition thing, aerosol pharmaceutical preparation should be homogeneous in the ability to do. About the aerosol pharmaceutical preparation which contains a solid as an active ingredient, it dissociates eventually and the active ingredient should form the suspended solid uniformly distributed with a propellant and other components of the drug product, for example, a solvent, or a surface-active agent. It is required for aerosol pharmaceutical preparation to receive uniformity of a certain kind generally, in this way, before carrying out container stuffing. Since aerosol pharmaceutical preparation contains the propellant which becomes a gas by a usual temperature and pressure (about 20degreeC and 1,013 hPa (1 atmosphere)), uniformity of aerosol pharmaceutical preparation may include a problem. In order to avoid volatilization-ization, aerosol pharmaceutical preparation must be dealt with with either of the temperature which is below a high pressure or the boiling point of aerosol pharmaceutical preparation.

[0004]The homogenizer ordinarily used according to the present way for uniformity of aerosol pharmaceutical preparation is provided with a stowage container and the propeller-like rotor which promotes to a stator the liquid accommodated in the container, and makes a liquid uniform. The homogenizer (a rotor / stator type homogenizer) which can be used now [of this design] does not act to the contents of the stowage container by a high pressure substantially. That is, the homogenizer of a rotor / stator type design can operate only by ambient pressure or a slightly high pressure, and this homogenizer cannot operate by sufficient high pressure to maintain a volatile material at that liquid state. In this way, if a process is carried out at the temperature below the boiling point of a propellant, it can use only for a rotor / stator type homogenizer uniforming the mixture containing a low-boiling-point volatile propellant. When it does not desire this, when this is impossible, it must appeal to other means as temperature with a low ingredient of aerosol pharmaceutical preparation like [when not being fully miscibility]. In such a situation, the non-volatile output concentrate which consists of an active ingredient and a liquid comparatively comparatively non-volatile with a high boiling point is manufactured in the first place. Since the output concentrate is comparatively non-volatile, this output concentrate can be uniformed using a rotor / stator type homogenizer by ambient air temperature and a pressure. Once it is uniformed, an output concentrate will be mixed with a propellant under a pressure, and will form homogeneous aerosol pharmaceutical preparation.

[0005]in this way -- as a propellant -- CFC12 (CCl_2F_2.) $\underline{T_b}$/**C=-29.8 or CFC114 ($C_2Cl_2F_4$.)

Inhalation aerosol pharmaceutical preparation of the drugs which contain low-boiling point chlorofluorocarbon (CFC) comparatively like $\underline{T_b}$/**C=3.8, it is, for example like [as the activator agent as a solid eventually divided into the 1st] CFC11 (CCl_3F, $\underline{T_b}$/**C=23.75) -- with CFC of a high boiling point comparatively. it is known in medicine manufacture technology that it can make by preparing the output concentrate containing a surface-active agent or suspension (for example, a soybean lecithin, oleic acid, and the span (Span) (registered trademark) -- in addition). This output concentrate can be uniformed by ambient air temperature and a pressure using a rotor / stator type homogenizer. Once it is uniformed, an output concentrate and a comparatively low-boiling-point CFC propellant will be introduced into a pressure vessel, and they will form the homogeneous pharmaceutical preparation which was mixed in this container and completed. Subsequently, bit equipment like the equipment of MDI which operates with either a high pressure and ambient air temperature or a low (filled up with a container, ranking second and attaching a lid) temperature and ambient pressure (the retrofilling is carried out through the valve of a container with a lid) is filled up with the completed pharmaceutical preparation.

[0006]In the pharmaceutical preparation mentioned above, CFC of a high boiling point is comparatively useful for three important and peculiar functions. CFC of a high boiling point serves [1st] as a solvent of suspension like a soybean lecithin. In order to secure an exact and reproducible dose, it is required for suspension to be able to dissolve thoroughly into an output (it is only CFC in which high boiling point CFC exists) concentrate, and (both high boiling point CFC and low-boiling point CFC exist) the whole pharmaceutical preparation. High boiling point CFC serves as quality of carrier fluid about the interaction of high boiling point CFC which has [2nd] solid drugs particles. High boiling point CFC serves as a cause of the carburetion pressure the whole last pharmaceutical preparation power the 3rd. The pressures of pharmaceutical preparation are one of the variables which influences optimization of the active-ingredient adhesion in a patient's lung, therefore the effect of pharmaceutical preparation. Since it is a result of contribution of the partial pressure of all CFCs by which the last carburetion pressure power of pharmaceutical preparation is used for pharmaceutical preparation in relation to this, high boiling point CFC is comparatively called a propellant.

TECHNICAL PROBLEM

[Problem to be solved by the invention]The concerns of the latest environment about use of a CFC propellant resulted in substitution of a hydronaliumfluorocarbon alkane (HFA) propellant instead of traditional CFC. It turned out that it cannot use for the method of having mentioned above which prepares the aerosol pharmaceutical preparation which attains uniformity using a rotor / stator type homogenizer by ambient air temperature and a pressure generally making the pharmaceutical preparation which used HFA as the base. There is no permissible high boiling point HFA in particular that can be used for making a non-volatile output concentrate so that it may be carried out in the case of the CFC pharmaceutical preparation using CFC11 mentioned above. Therefore, low-boiling point HFA, an activator agent, a surface-active agent, and the homogeneous mixture of other components of the drug product must be made. It is clear that it is a high pressure or uniformity of the pharmaceutical preparation containing low-boiling point HFA must be performed at a low temperature. Otherwise, it is because low-boiling point HFA evaporates. However, since the surface-active agent of a large number which do not cause HFA and a chemical reaction cannot dissolve in HFA pharmaceutical preparation at a low temperature, uniforming at a low temperature is not necessarily possible. Therefore, uniformity must be performed at a high temperature.

[0008]A misfortune is used, and as mentioned above, the rotor / stator type homogenizer which operates under sufficient pressure to prevent volatilization of low boiling point components like a propellant do not exist now. Therefore, the existing technology cannot be used for uniforming the pharmaceutical preparation containing low boiling point components like a HFA propellant with ambient air temperature. As further background, when the particle of an active substance should make it become muddy in aerosol pharmaceutical preparation, such particles are dramatically small and he should understand that it must have uniform particle diameter substantially. That is, in order to form a homogeneous suspended solid, the particles of an active ingredient must be superfines-ized. Such superfines-ization is attained by the grinding work usually done before mixing an active substance to pharmaceutical preparation. Since they are in the tendency which generates **** of the active substance showing expensive waste of activity material, manage still more difficult by polluting a production environment by **** of this active substance and cause a worker's risk of happening, such grinding work is not desirable. Since it is wished, however conventional technology does not provide the method or equipment which can be superfines-ized, for example after mixing a solid active substance to aerosol pharmaceutical preparation between uniformity stages as a result, the conventional grinding may be avoided.

MEANS

[Means for solving problem]According to the purpose and other purposes of becoming clear succeedingly which were mentioned above, this invention is dispatched to the closed equipment which uniforms the aerosol pharmaceutical preparation which has the following elements and which can be pressurized.
(1) Mixing vessel which has an inlet means and an outlet means and which can be pressurized;
(2) It has a homogenizer arranged by carrying out fluid communicating to a reaction vessel, Said homogenizer is provided with two or more nozzles which have a long and slender orifice which ejects the sheet under the pressure of the liquid which should be uniformed, Said nozzle is arranged so that the turbulent flow jet interaction of said sheet may be made to perform along with the anterior part of a common jet interaction, Said sheet is ejected by said nozzle along with the anterior part of a common liquid ejection interaction in the low pressure zone region filled with said liquid of said sheet, and said sheet, The common boundary constituted and formed with said sheet intrinsically ejected in said said mixture of the area within a low pressure zone and said low pressure zone region is met, A turbulent flow jet interaction in said low pressure zone region filled with said liquid caused further by said nozzle. A means to constitute the jet interaction room constituted so that said low pressure zone region of said liquid organization which is ejected and makes the; aforementioned turbulent flow jet interaction perform might be provided, and a means to eject said liquid organization under; pressure for said nozzle;
(3) It returns from [from said exit of said mixing vessel to a homogenizer] a homogenizer to the entrance of a mixing vessel, and has a fluid lead pipe which forms closed equipment among them.
[0010]This invention is provided with the following.
The process as which it is sent to how to uniform the aerosol pharmaceutical preparation in a closed continuation loop device under a high pressure, and this method determines the level of a request of uniformity.
The process of mixing the aerosol pharmaceutical preparation in a mixing vessel.
The process which circulates the aerosol pharmaceutical preparation mixed with the high voltage homogenizer.
The process which operates a high voltage homogenizer by sufficient pressure to attain uniformity of the mixed aerosol pharmaceutical preparation, the process which is made to circulate through aerosol pharmaceutical preparation and is returned into a mixing vessel, and the process of repeating the above-mentioned process until it attains uniformity of a predetermined level.
A closed continuation loop device is good to connect with the high voltage filling station filled up with aerosol pharmaceutical preparation by connecting mechanism and a duct means. In the embodiment of a modification, when diluting aerosol pharmaceutical preparation with an aerosol propellant to the aerosol pharmaceutical preparation of predetermined volume, a closed continuation loop device is good to use for preparing the condensed aerosol pharmaceutical preparation which is transported to a large container by a connecting mechanism nozzle conduit means.
[0011]
[Objects of the Invention]Therefore, the purpose of this invention is to provide the improved method and equipment which uniform a volatile mixture. The further purpose of this invention is ambient air temperature, and there is in providing the method and equipment which uniform a

volatile mixture, for example, the aerosol pharmaceutical preparation containing a low-boiling point HFA propellant. In addition, supposing the further purpose is processed at a low temperature of this invention, there is in providing the method and equipment which enable preparation of aerosol pharmaceutical preparation which has a wide range surface-active agent containing the surface-active agent which cannot be mixed with dispensing. The purpose of further others of this invention provides the method and equipment of superfines-izing the particles of the active substance in aerosol pharmaceutical preparation, and uniforming aerosol pharmaceutical preparation which are both made, and there is in removing the demand of the conventional pulverizing of an active substance.

[0012]Other purposes of this invention will become clear still more easily, when they consider detailed explanation of the following of the desirable embodiment of this invention about an accompanying drawing. The structure of this invention, an operation, and an advantage will become clear when they take into consideration non-limiting explanation of the following of some embodiments of this invention about an accompanying drawing.

[0013]

[Mode for carrying out the invention]Reference of drawing 1 will show a 1st embodiment of the equipment of this invention. Generally, the equipment of this invention is provided with the connector 30 (a) which connects the component parts of the mixing means 40 with the lead pipes 31, 32, 33, and 34, and 30 (b) in order to form the mixing vessel 10 provided with the mixing means 40, the high voltage homogenizer 12, and a closed continuation loop device. Once it is sealed, the whole equipment can process with equipment the aerosol pharmaceutical preparation which operates under a pressure and contains a volatile propellant with ambient air temperature. The mixing vessel 10 is constituted so that aerosol pharmaceutical preparation may be accommodated, and it has a crowning (not shown) with which a mixing vessel is made to load and which can be removed. As for the mixing vessel 10, it is good that it is a 3785 cubic centimeters (1 gallon) stirring type floor lamp reactor of the pearl (Parr) model 4550 for example.

[0014]The high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain instantaneous superfines-ization of the particle in aerosol pharmaceutical preparation, when it can apply with uniformity and is wanted. As for the high voltage homogenizer 12, it is good that it is micro fluidics (Microfluidics) model M-110F Micro fluidizer (Microfluidizer) (registered trademark) for example. The equipment and the operating method of a Micro fluidizer (registered trademark), It is explained to US,4,908,154,B published in Cook (Cook) etc. on US,4,533,254,B published in Cook (Cook) etc. on August 6, 1985, and March 13, 1990 still in detail, and they are used here. The brief explanation of an operation of the homogenizer 12 is as follows. The homogenizer 12 has the entrance 13 connected with the high pressure pumping 15 with the lead pipe 32, has the pressure surveillance gauge 17 attached to the exit pipe 33, and propels material under a pressure by the jet interaction room block means 18. The fixed procedure of grinding of particles, distribution, and uniformity happens in the interaction interior of a room. Three different power which attains a required result, i.e., shearing, impaction, and a cavitation are used for the jet interaction room block means 18.

[0015]If a fluid flow is promoted into the interaction room 18 with high voltage, a fluid flow will go into the interaction room entrance 19, and will be divided into the two laminar flow 22 and 23 by the flow splitter 20. Each flow goes into the channel (not shown) of a jet interaction room block. A channel is formed by machining a slot into two blocks which faced each other and fitted in exactly. Shearing force is applied to the fluid flow in alignment with the wall of a channel. A

channel pulls apart each laminar flow mutually, and it ranks second, and it is constituted so that it may draw near mutually. The flows 22 and 23 gather in the impaction room 28, and collide mutually with high voltage in the space which has comparatively larger cross sectional area and volume than the cross sectional area and volume of two channels. A fluid flow is made to produce a cavitation by this rapid change of a cross sectional area and volume. Moreover, two flows produce impaction from it being [being high voltage and] high-speed, and colliding mutually. The produced flow is uniformed and any particles in pharmaceutical preparation are superfines-ized. The produced flow leaves the interaction room 18 from the interaction room exit 29, and is returned to the mixing vessel 10 via the connector 14 with the lead pipe 34.

[0016]The homogenizer which has the structure mentioned above superfines-izes the organic drugs compound suspended into the liquid. The grade of uniformity, i.e., reduction of particle diameter, is controllable by the length of the time which circulates the inside of equipment [fluid flow / containing the size and the particle of the energy input from the pump 15, and the channels 22 and 23]. Other factors which determine the effect of processing have the peculiar character, for example, the hardness, the viscosity, others, and the relation of a specific material processed. The component parts of closed equipment are connected by the connector 30 (a) and 30 (b), and these connectors suit the pressure of equipment, and the ingredient and chemical reaction of aerosol pharmaceutical preparation are not caused. As for the connector 30 (a) and 30 (b), it is good that they are stainless steel, a plastic, or a rubber tube for example. The connector 30 (a) and each of 30 (b) are good optionally to finish with "rapid connection" coupling, and, as a result, can carry out an assembly and decomposition for equipment easily.

[0017]The connector 30 (a) and 30 (b) serve as a means to connect a lead pipe with an element of equipment. An active ingredient and a required surface-active agent, or other components of the drug product are added to the mixing vessel 10 except for a volatile component during use. Typically, the mixing vessel 10 has a lid (not shown) which can remove [that sealing which can be removed in order to introduce these components of the drug product into a container with a sufficient condition is possible, and]. Once these non-volatile ingredients are introduced, the mixing vessel 10 will be sealed. An active ingredient is good to include an effective quantity pharmaceutically [a respiratory compound of activity] pharmaceutically for example. An active ingredient contains ipratropium bromide and the aldbuterol sulfate (albuterol sulfate), for example. An active ingredient may be a superfines-ized form or may be a form which has not been superfines-ized.

[0018]A possible surface-active agent Acetylation monoglyceride like isopropyl myristate and MIBASETTO (Myvacet (registered trademark)) 9-08 for example, Perfluoro-carboxylic acid (perfluorocarboxylic acid), A polyethylene glycol (PEG200, 300 and 400, or 600), A polyethylene oxide sorbitan fatty acid ester (Tween (Tween (registered trademark)) 20, 40, 60, 65, and 80 or 85), Sorbitan ester, such as sorbitan monolaurate, sorbitan monooleate, and sorbitan palmitate, a polyvinyl pyrrolidone (K17;K25;K30 or K90), propylene glycol, and oleic acid are included. A surface-active agent is good to add 0.1 to 0.5weight % of quantity, or more based on gross weight of a constituent. The total amount of a surface-active agent should be less than about 3 weight %.

[0019]When aerosol pharmaceutical preparation is sensitive to moisture and air, before putting aerosol pharmaceutical preparation into a mixing vessel, it is necessary to purge equipment with super-high-purity nitrogen. A propellant is supplied to the reaction vessel 10 under a pressure from the entrance 11 with a valve. A propellant, for example Low boiling point hydrocarbon (1, 1, 1, 2, 3, 3, and 3-heptafluoro propane), i.e., HFA-227, It is good that they are HFA-134a

(tetrafluoro ethane) or HFA-227 and a HFA propellant like the compound of HFA-134a, CFC12, CFC propellants like 114, or those mixtures. A propellant is good to include a solvent, for example, alcohol like ethanol. Although an output concentrate can be made, according to environment, it is not necessary from the process of this invention to make. When working in batch (about 3 l. of pharmaceutical preparation) of a small laboratory scale, it is in good order to uniform directly the components of the drug product which have the quantity of sufficient propellant to jump over the process of making an output concentrate and make perfect pharmaceutical preparation. (For example, 3 l. is exceeded) About a large-scale batch, it is preferred to make a homogeneous output concentrate, to rank second and to dilute it with an additional propellant suitably.

[0020]If all the ingredients of aerosol pharmaceutical preparation are once in the mixing vessel 10 and a mixing vessel is pressurized by 552 kilopascals (from 70 psi to 80 psi) from about 483 kilopascals, aerosol pharmaceutical preparation will be ready for mixing, uniformity, and superfines-izing. Mixing is attained by the agitating equipment 40 arranged in the mixing vessel 10. As for the agitating equipment 40, being set as speed of about 400 rpm is preferred. While the contents of the mixing vessel are once stirred completely and agitating equipment is still operating,; pharmaceutical preparation which opens the outlet valve 50 and is made to circulate pharmaceutical preparation through the inside of equipment in following order, It flows from the mixing vessel 10 in the valve 50, the connector 30 (b), and the homogenizer 12, and it ranks second and returns from the connector 30 (a) to the mixing vessel 10. The mixing vessel 10 is optionally provided with the drain 51 which makes easy washing of a mixing vessel, or removal of the remaining output.

[0021]Pharmaceutical preparation is ipratropium bromide (it superfines-ized). 45.0 g Isopropyl myristate It is good to include 75.0 g 1, 1, 1, 2, 3, 3, and 3-heptafluoro propane 74.88-kg*.

* During restoration, this quantity contains a surplus amount of a propellant introduced while processing in order to compensate a steam which remains in a sealed manufacture tank, when decreasing a liquid increase-in-quantity suspended solid. It is good to add super-high-purity nitrogen to the mixing vessel 10 from the valve 9, and to bring a reaction vessel pressure up to about 689 kilopascals (100 psi). This superfluous pressure assists circulation of aerosol pharmaceutical preparation in equipment.

[0022]When an active ingredient used as a starting material is a liquid or the already superfines-ized solid, the high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain uniformity of aerosol pharmaceutical preparation. When an active ingredient used as a starting material is a solid which is not superfines-ized, the high voltage homogenizer 12 acts on aerosol pharmaceutical preparation by sufficient pressure to attain instantaneous superfines-izing and uniformity of aerosol pharmaceutical preparation. A part depends on active-ingredient itself for a pressure used for uniformity, superfines[instantaneous]-izing, and uniformity. A certain active ingredient may take a still higher pressure and still longer processing time to attain a result of a request with peculiar character of those crystal structures.

[0023]For example, when the superfines-ized active ingredient is used as a starting material, typically, the high voltage homogenizer 12 is set up supply the pressure of about 55,158 to 62,053 kilopascals (from 8,000 psi to 9,000 psi) to aerosol pharmaceutical preparation. Supposing the active ingredient which is not superfines-ized is used as a starting material as a modification, typically, the means 12 for high voltage uniformity and superfines-izing will be set up give the pressure of about 137,895 kilopascals (20,000 psi) to aerosol pharmaceutical

preparation. aerosol pharmaceutical preparation -- the level of a request of uniformity -- applicable -- if it becomes, it will circulate until the level of a request of superfines-izing is attained. Typically, this needs the passage of at least ten volume exchange in equipment.
[0024]It is good during the operation of the high voltage homogenizer 12 to have the means 60 for cooling the high voltage homogenizer 12. As for this means 60, it is good that they are an ice bath or a refrigeration unit for example. This is performed in order to prevent accumulation of the superfluous heat produced from the impaction of high-speed particles and particles produced within the high voltage homogenizer 12. By the cooling method 60, in order to maintain a pressure below to about 1,034 kilopascals (150 psi), the temperature and the pressure of the high voltage homogenizer 12 are reduced. According to one embodiment, by the cooling method 60, while a high voltage homogenizer and the micronizer 12 are in use, the pressure to about 16degreeC is reduced for the temperature of a homogenizer up to about 586 kilopascals (85 psi). When the process of uniformity or instantaneous superfines-izing, and uniformity is completed, as for aerosol pharmaceutical preparation, preparation of a bit process is completed. The bit of the completed aerosol pharmaceutical preparation is carried out into a container by two different methods. When the completed pharmaceutical preparation is not injured by cold, pharmaceutical preparation is cooled below at that boiling point, it ranks second, and while being taken out from the application-of-pressure homogenizer of this invention works at a good and still low temperature, the open container is filled up, it ranks second and a lid is attached to this container. Drawing from the pressurizer of this invention is performed by connecting the exit of the mixing vessel 10 with a suitable dispenser, using ordinary technology, the known small amount of an aerosol composition is sent out to an aerosol can, a lid is attached to this aerosol can, and this dispenser is sealed.
[0025]When producing as a modification reduction of quantity of a surface-active agent which can dissolve in pharmaceutical preparation by cooling of pharmaceutical preparation, restoration of a container must be performed by ambient air temperature and a high pressure using closed equipment. Other embodiments of this invention explained below function this latter. Reference of drawing 2 will show a 2nd embodiment of this invention. Although this is the same as that of a 1st embodiment, it has an additional means for operating under a high pressure by uniforming, carrying out the bit of the superfines-ized aerosol pharmaceutical preparation into a container sealed by the Klin ping, supposing it is applicable, and carrying out the retrofilling from a valve of a container with a lid simultaneously. A common reference number is applied to the same items, and as mentioned above, it operates. For example, if drawing 2 is continued and referred to, as mentioned above, it will add to the mixing vessel 10, the high voltage homogenizer 12, the connector 30 (a), and 30 (b), Equipment is further provided with the three way valve 100, the pump 70, other three way valves 101, the by-pass line loop 110, the entrance check valve 120, the dispenser 80, the exit check valve 130, and the pneumatic pressure bypass valve 90. Optionally, equipment is good to have further the serial flow instruments 170 and 171 which supervise a flow of pharmaceutical preparation through the whole processing loop.
[0026]The pump 70 constitutes a means for circulating aerosol pharmaceutical preparation in equipment among operating time of equipment, when pharmaceutical preparation separates and is shunted from a homogenizer and the micronizer 12. As for the pump 70, it is good that it is micropump (Micropump) (registered trademark) model 152-000 magnetic pumping for example. The by-pass line loop 110 provides a channel which circulates aerosol pharmaceutical preparation, when aerosol pharmaceutical preparation is not turned to the dispenser 80. The by-pass line loop 110 is good to be made by inactive plastic or a tube of rubber by a stainless steel

tube or material processed. The dispenser 80 is a means for carrying out the bit of the aerosol pharmaceutical preparation into an aerosol can. As for the dispenser 80, it is good that they are PAMAZORU (Pamasol)(registered trademark) 2016 / 1 pressure filling machine for example.
[0027]The serial flow instrument 170 is good to be arranged just behind the three way valve 100, and to arrange other serial flow instruments 171 just before the reaction vessel 10. An operation of equipment provided by 2nd embodiment of this invention except for a transfer of pharmaceutical preparation into a container sealed by the Klin ping processed thoroughly is the same as that of a 1st embodiment. That is, supposing equipment is loaded with an active ingredient, a propellant, and other components of the drug product, pharmaceutical preparation is uniformed by same method as having mentioned above with reference to a 1st embodiment and it is applied, a solid active ingredient will be superfines-ized. Equipment provided by 2nd embodiment separates pharmaceutical preparation processed thoroughly from the homogenizer 12, and it differs from a 1st embodiment in that it has an added component made to be turned to a direction of the dispenser 80 a container can be filled up with pharmaceutical preparation.
[0028]While carrying out the process of uniformity or instantaneous superfines-izing, and uniformity, :pharmaceutical preparation which flows in the element of the embodiment shown in drawing 2 in order of the following [pharmaceutical preparation / aerosol] leaves the mixing vessel 10, The drain valve 50, the lead pipe 30 (c), the three way valve 100, the lead pipe 30 (d), the high voltage homogenizer 12, the lead pipe 30 (e), It flows in the three way valve 101, the lead pipe 30 (f), the optional flow instrument 170, lead pipe 30(i), the bypass connector 110, the open bypass valve 90, the lead pipe 30 (n), the optional flow instrument 171, and the lead pipe 30 (o), and it ranks second and returns into the mixing vessel 10. once -- uniformity -- applicable -- if it becomes and superfines-ization will be completed, the flow of pharmaceutical preparation will be diverted from the homogenizer 12 to the pump 70 by the operation of the three way valves 100 and 101 with the lead pipe 30 (g) and the lead pipe 30 (h). The high voltage homogenizer 12 is removed from the circulation flow passage of aerosol pharmaceutical preparation, in order to avoid superfluous processing of aerosol pharmaceutical preparation. As for this time, the pump of the high voltage homogenizer 12 caused circulation of the pharmaceutical preparation in equipment. Once the flow of pharmaceutical preparation is diverted from the high voltage homogenizer 12, the pump 70 will take over this work. Like the agitating equipment 40 of the reaction vessel 10, the pump 70 does sufficient stirring so that a suspended solid may be maintained. When both the temperature after circulation with the pump 70 for about 15 minutes and in a container and a pressure increase to the value near those first values, it is good for a bit to start.
[0029]The bit of pharmaceutical preparation is controlled by concurrent operation of the two check valves 120 and 130 and the pneumatic pressure bypass valve 90. It is filled up with the pharmaceutical preparation of the volume which opened the entrance check valve 120 and the exit check valve 130, set up the pneumatic pressure bypass valve 90 close the bypass 110, circulated the inside of the lead pipe 30 (j) and the valve 120, and was beforehand set as the dispenser 80 in pharmaceutical preparation by that cause in order to begin a bit process. Once it fills up, excessive pharmaceutical preparation will leave the dispenser 80 and will flow backwards to a reaction vessel through the lead pipe 30 (q), the open check valve 130, the lead pipe 30 (m), the bypass valve 90, the lead pipe 30 (n), the optional flow instrument 171, and the lead pipe 30 (o). The aerosol can which a lid is attached and has a suitable valve is filled up with aerosol pharmaceutical preparation. The valve of the container with which it should be filled up is pressed fit and liquid free passage connection is carried out with the port 85 with a valve of the

dispenser 80. Thereby, the pharmaceutical preparation of the volume in the dispenser 80 set up beforehand is made to blow off from the dispenser 80, and the retrofilling is carried out through the valve of a container.

[0030]When pressing the valve of a container fit and carrying out liquid free passage connection with the port 85 of the dispenser 80, it closes automatically, the pneumatic pressure bypass valve 90 is reset automatically, and the entrance check valve 120 and the exit check valve 130 enable passage in the bypass 110 of pharmaceutical preparation. In this way, the flow of pharmaceutical preparation is detached and diverted from the dispenser 80, and the flow of pharmaceutical preparation fills a container simultaneously. By demounting the filled container from liquid free passage connection in the port 85 of the dispenser 80, the two check valves 120 and 130 are opened automatically, close the pneumatic pressure bypass valve 90 simultaneously, and enable pharmaceutical preparation to flow in the dispenser 80. The dispenser 80 is re-loaded with the pharmaceutical preparation of the quantity set up beforehand by this, and the preparation filled up with other containers is completed in the dispenser 80.

[0031]Drawing 3 and especially drawing 4 illustrate simultaneously other embodiments of this invention applicable to production of a large batch of aerosol pharmaceutical preparation, i.e., a batch of an industrial scale. A common reference number is applied to the same items, and as mentioned above, it operates. For example, the mixing vessel 10 and the; drain valve 50 in which manufacture of a batch of an industrial scale and equipment of this invention which carries out a bit have the mixed adjustable vane 40, and the; lead pipe 30 (a) and; high voltage homogenizer 12; it has the additional lead pipe 30 (b),; return-line coupler 160, and; return-line valve 150. As shown in drawing 4, the pharmaceutical preparation container 140 holds aerosol pharmaceutical preparation for a bit process. As for the pharmaceutical preparation container 140, it is good that it is a well-closed container of stainless steel for example. The return-line coupler 160 is a means for connecting an end of the lead pipe 30 (b) with either the reaction vessel (as [show / in drawing 3]) 10, or (as [show / in drawing 4]) the pharmaceutical preparation container 140. For example this coupler 160 constitutes what is called a rapid connection coupler of a lot, and is used for a male coupler making the lead pipe 30 (b) finish, and a corresponding female coupler in which doubling is possible exists as a port to the containers 10 and 140.

[0032]Like [in case connection is switched to another side from one side], the return-line valve 150 constitutes the means for closing the flow of pharmaceutical preparation, when the lead pipe 30 (b) is connected with the container 10 or neither of 140. Since what is called a rapid connection coupler has a valve of one closed automatically when two half parts of coupling are separated, it is [the return-line valve 150] in good order to be contained as an integral part of the connecting mechanism 160. It is good to carry out using the embodiment of the invention which are uniformity of aerosol pharmaceutical preparation, and the method substantially same supposing it is applicable as the embodiment which shows drawing 1 superfines-ization, and is shown by drawing 3 and drawing 4. That is, the reaction vessel 10 is filled with the non-volatile ingredient which must be in the active ingredient (this active ingredient may be superfines-ized or it is not necessary to superfines-ize it if it is a solid) of desired quantity, arbitrary surface-active agents, a solvent, or pharmaceutical preparation. Subsequently, a container is sealed and a propellant is introduced under a pressure from the port 11 with a valve. However, it is preferred to introduce a quantity smaller than all the quantity of the propellant needed for constituting the completed pharmaceutical preparation in the case of large batch, i.e., batch of an industrial scale. In this way, it is preferred to make an output concentrate first and this output concentrate can be processed with the homogenizer 12 still more easily than the completed pharmaceutical

preparation which contains all the quantity of a propellant according to that volume not being comparatively large. Superfines-ization is performed by uniformity and the equipment constituted as it was shown in drawing 3, supposing it was applicable, and this equipment is functionally [as the equipment shown by drawing 1] equivalent. The operation of the equipment constituted as shown in drawing 3 is the same as that of the embodiment shown in drawing 1.
[0033]For a bit process, the drain valve 50 of the reaction vessel 10 is bolted to the high voltage homogenizer 12. Subsequently, the aerosol pharmaceutical preparation which was superfines-ized and was uniformed is made to transport to the pharmaceutical preparation container 140 by the procedure of explaining below. The return-line valve 150 between the high voltage homogenizer 12 and a reaction vessel is closed. The high voltage homogenizer 12 is terminated. All aerosol pharmaceutical preparation should be in the reaction vessel 10. As for the return-line coupler 160, engagement is canceled of the reaction vessel 10. Reference of drawing 4 will connect the return-line coupler 160 with the pharmaceutical preparation container 140. The drain valve 50 is made to lead to the high voltage homogenizer 12, and high-pressure uniformity and superfines-izing are started. Aerosol pharmaceutical preparation is transported to the pharmaceutical preparation container 140 by a high pressure from the reaction vessel 10. The agitating equipment 180 of the pharmaceutical preparation container 140 is made to start. When almost all aerosol pharmaceutical preparation is transported, the drain valve 50 of the reaction vessel 10 is closed, and the high voltage uniformity unit 12 is terminated.
[0034]As for the procedure of a rinse, it is preferred that it is as follows. The propellant (in the case of a 3.8L mixing vessel, 3 l. or less is preferred) of a certain quantity for rinsing the mixing vessel 10 is added to the mixing vessel 10. The volume for [of a propellant / this] rinsing is preferably stirred in about 5 minutes and within the container 10. The drain valve 50 of the mixing vessel 10 is made to lead to the high voltage homogenizer 12, and the high voltage homogenizer 12 is made to start. The high voltage homogenizer 12 feeds the volume which a propellant rinses in the pharmaceutical preparation container 140. It is preferred to cause much more many of these procedures of several times to rinse. It is preferred to use at least 4 times of the procedures to rinse. When a rinse is completed, by the inlet port 141 with a valve, the remaining quantity of the propellant which takes aerosol pharmaceutical preparation to bring to the last aerosol pharmaceutical preparation is made to act under a pressure, and is quantitatively applied to the pharmaceutical preparation container 140. The agitating equipment 180 of the pharmaceutical preparation container 140 continues operating.
[0035]And it is good to fill up each container using the technology which mentioned above the aerosol pharmaceutical preparation in a pharmaceutical preparation container. That is, it is ambient air temperature, and while acting at the temperature below the boiling point of a propellant and the pharmaceutical preparation which carried out the bit, it is good to transport pharmaceutical preparation to an open container from the container 140, to rank second and to seal this open container using a lid and a valve assembly. As a modification, while acting by ambient air temperature and a high pressure, it is good to fill up a container with a lid with the pharmaceutical preparation in the container 140 using a dispenser like the means 80 built into the embodiment shown in drawing 2. Various aerosol pharmaceutical preparation was made using the manufacturing process of the batch of this industrial scale. For example, the aerosol pharmaceutical preparation of ipratropium bromide / HFC-227, and aldbuterol sulfate / HFC-227 were manufactured using the process of this invention. In addition, the ipratropium bromide / HFC-227 using the active ingredient which has not been superfines-ized were manufactured using the process of this invention.

EXAMPLE

[Working example]According to the following working examples, the desirable embodiment of this invention within the limits is described further, and is proved. Although these working examples belong to the aerosol pharmaceutical preparation for medical application, this invention is suitable also for application of other industries, for example, a paint, cosmetics, and a deodorant. Since it is possible to carry out many modification of this invention, without deviating from the pneuma and the range of this invention, these working examples are given for the purpose of illustration, and should not be interpreted as what limits this invention.
(Working-example 1-4) The working example 4 shows the MDI pharmaceutical preparation which prepared the superfines-ized active ingredient from the ingredient of the following used as a starting material with reference to drawing 2 from the following working examples 1, using the method and equipment of this invention.
[0037]
[Table 1]Table 1. ----------. An working example An active ingredient A surface-active agent A propellant. ----------. 1 Superfines-ized --- HFC-227 ipratropium bromide. ----------. 2 It superfines-ized. --- HFC-227 aldbuterol sulfate. ----------. 3 It superfines-ized. Isopropyl HFC-227 ipratropium bromide Millis Tait. ----------. 4 superfines-ized oleic acid and HFC-227 ipratropium bromide a span -- and -- and -- Superfines-ized isopropyl Aldbuterol sulfate Millis Tait. It added to the reaction vessel 10 with quantity calculated so that a therapy dose might be given, when positioning a constituent for a ---------- ---------- active ingredient to an aerosol can with a throttle valve, and a required surface-active agent. a surface-active agent -- about 3 or less weight % of an effective dose -- it added. It added to the reaction vessel 10 which sealed a reaction vessel and sealed super-high-purity nitrogen. Super-high-purity nitrogen was added and it came that it was up to 348 kilopascals (50 psi) about the last reaction vessel pressure. With super-high-purity nitrogen, a pressure in the reaction vessel 10 was purged slowly. A purge was stopped when a reaction vessel pressure decreased up to 69 kilopascals (10 psi).
[0038]The propellant was supplied to the reaction vessel 10. Super-high-purity nitrogen was added to the reaction vessel 10, and it came that it was up to 689 kilopascals (100 psi) about a reaction vessel pressure. The agitating equipment 40 of the reaction vessel 10 was started, and it was set as speed of 400 rpm. Stirring was continued for about 15 minutes before the process of continuing. While the agitating equipment 40 was operating at 400 rpm in addition, the drain valve 50 of the reaction vessel 10 was made to lead to the high voltage homogenizer 12. H_2O obtained by a small quantity distilling was placed into the pressure intensifier pump of the high voltage homogenizer 12, in order to carry out the lubrication of the seal. The added water did not have influence harmful to the stability in early stages of pharmaceutical preparation with the water which did not rise [of the manufactured aerosol] notably and was added. The high voltage homogenizer 12 was set up about the homogenizing step supply the pressure of 55158 kilopascals (8000 psi) to aerosol pharmaceutical preparation.
[0039]The inside of the following elements was circulated for aerosol pharmaceutical preparation in an order.
reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(d); high voltage homogenizer 12; -- three way valve 101; besides lead pipe 30 (e); -- lead pipe

30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i); bypass loop 110. or lead pipe 30 (j) and entrance check valve 120, dispenser 80 and exit check valve [either one of] 130; -- a lead pipe -- 30(m); pneumatic pressure bypass valve 90; -- it returns into lead pipe 30 (n); and the reaction vessel 10, and operating agitating equipment was continued within the reaction vessel 10 This was all the circulation flow passages of the aerosol pharmaceutical preparation about a homogenizing step. The whole equipment was bolted to outside environment. Processing frequency of ten volume exchange was carried out. The ice bath was held in the heat exchanger of the parts of a high voltage homogenizer and the micronizer 12 during the operation of the homogenizer 12. By it, vessel temperature decreased to 16degreeC and maintained the pressure to 586 kilopascals (85 psi) during the operation of the high voltage homogenizer 12.
[0040]The bit process is as follows. By diverting the three way valve 100 from the high voltage homogenizer 12 to the pump 70, the high voltage homogenizer 12 was demounted from the circulation flow passage. For the bit process, the inside of the following elements was circulated for aerosol pharmaceutical preparation with the pump 70 in an order.
reaction vessel 10; drain valve 50; -- a lead pipe -- 30. the bypass loop 110 or the entrance check valve 120, the dispenser 80, and the lead pipe 30 (q); (c) --; three way valve 100; -- a lead pipe -- 30(g); pump 70; -- three way valve 101; besides lead pipe 30 (h); -- lead pipe 30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i). either one of [and] the exit check valve 130 or a lead pipe (m) 30 --; pneumatic pressure bypass valve 90; -- it returned into lead pipe 30 (n); and the reaction vessel 10. This was all the circulation flow passages of the aerosol pharmaceutical preparation which a bit process attaches. Aerosol pharmaceutical preparation was circulated for 15 minutes with the pump 70. Subsequently, the bit of the aerosol pharmaceutical preparation was carried out into the can of MDI. When circulating aerosol pharmaceutical preparation, the container with a valve which carried out crimp has been arranged under the valve port 85 of the dispenser 80. The aerosol pharmaceutical preparation of the volume set up beforehand was supplied to the container. When pushing the valve port 85 on the valve of a container, the entrance check valve 120 and the exit check valve 130 are closed automatically, the pneumatic pressure bypass valve 90 is opened, and the channel for the aerosol pharmaceutical preparation which still circulates through the inside of equipment is provided.
[0041](Working-example 5-8) The working example 8 shows the MDI pharmaceutical preparation which prepared the superfines-ized active ingredient from the ingredient of the following used as a starting material with reference to drawing 2 from the following working examples 5, using the method and equipment of this invention.
[0042]
[Table 2]Table 2. ----------. Working example Active ingredient Surface-active agent Propellant. ----------. 5 --- Freon 12 / 114 ipratropium bromide superfines-ized Mixture. ----------. 6 Superfines-ized soybean Freon 11 and ipratropium bromide Lecithin It reaches Freon 12. Freon 114 mixture. ----------. 7 The --- HFC-227 ipratropium bromide which has not been superfines-ized. ----------. 8 --- HFC-227 which has not been superfines-ized -- the aldbuterol sulfate ---------- ---------- active ingredient and the required surface-active agent were added to the reaction vessel 10. It is preferred about 3 or less weight % of quantity and to add a surface-active agent. It added to the reaction vessel 10 which sealed the reaction vessel and sealed super-high-purity nitrogen. Super-high-purity nitrogen was added and it came that it was up to 348 kilopascals (50 psi) about the last reaction vessel pressure. With super-high-purity nitrogen, the pressure in the reaction vessel 10 was purged slowly. The purge was stopped when a reaction

vessel pressure decreased up to 69 kilopascals (10 psi).
[0043]The propellant was supplied to the reaction vessel 10. Super-high-purity nitrogen was added to the reaction vessel 10, and it came that it was up to 689 kilopascals (100 psi) about a reaction vessel pressure. The agitating equipment 40 of the reaction vessel 10 was started, and it was made speed of 400 rpm. Stirring was continued for about 15 minutes before the process of continuing. While the agitating equipment 40 was operating at 400 rpm in addition, the drain valve 50 of the reaction vessel 10 was made to lead to the high voltage homogenizer 12. H_2O obtained by a small quantity distilling was placed into the pressure intensifier pump of the high voltage homogenizer 12, in order to carry out the lubrication of the seal. It did not have influence harmful to the stability in early stages of pharmaceutical preparation with the water which did not rise [of the manufactured aerosol] notably with the added water, and was added. The high voltage homogenizer was set up about superfines-izing and a homogenizing step give the pressure of 137,895 kilopascals (20,000 psi) to aerosol pharmaceutical preparation.
[0044]The inside of the following elements was circulated for aerosol pharmaceutical preparation in an order.
reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(d); high voltage homogenizer 12; -- three way valve 101; besides lead pipe 30 (e); -- lead pipe 30 (f); -- optional flow instrument 170; -- a lead pipe -- 30(i); bypass loop 110. exit lead pipe 30 (j) and entrance check valve 120 or dispenser [and] 80, lead pipe 30 (q), or check valve 130 or; -- a lead pipe -- 30(m); pneumatic pressure bypass valve 90; -- it returns into lead pipe 30 (n); and the reaction vessel 10, and operating agitating equipment was continued within the reaction vessel 10 This was all the circulation flow passages of simultaneous superfines-izing and the aerosol pharmaceutical preparation about a homogenizing step. The whole equipment was bolted to outside environment. The processing time of ten volume exchange was used. The ice bath was held in the heat exchanger of the parts of the high voltage homogenizer 12 during the operation of the homogenizer 12. By it, vessel temperature decreased to 16degreeC and maintained the pressure by 586 kilopascals (85 psi) during the operation of the high voltage homogenizer 12.
[0045]The bit process is as follows. By diverting the three way valve 100 from the high voltage homogenizer 12 to the pump 70, the high voltage homogenizer 12 was demounted from the circulation flow passage. For the bit process, the inside of the following elements was circulated for aerosol pharmaceutical preparation with the pump 70 in an order.
reaction vessel 10; drain valve 50; -- a lead pipe -- 30(c); three way valve 100; -- a lead pipe -- 30(g); pump 70; -- three way valve 101; besides lead pipe 30 (h); -- a lead pipe -- the 30(i); above-mentioned of was done -- as -- the bypass loop 110 or the dispenser 80. Aerosol pharmaceutical preparation was circulated for 15 minutes with the micropump 70. Subsequently, the bit of the aerosol pharmaceutical preparation was carried out into the can of MDI. Using the suitable valve, these containers attached the lid and crimp had already been carried out. When circulating aerosol pharmaceutical preparation, the container with a valve which carried out crimp was arranged under the valve port 85 of the dispenser 80. The aerosol pharmaceutical preparation of the volume set up beforehand was supplied to the container. When pushing the dispenser 80 on the valve of a container, the entrance check valve 120 and the exit check valve 130 are closed automatically, the pneumatic pressure bypass valve 90 is opened, and the channel for the aerosol pharmaceutical preparation which circulates through the inside of equipment in addition is provided.
[0046](Comparative example 4) When the Micro fluidizer (registered trademark) of micro fluidics is used as the high voltage homogenizer and the micronizer 12 for uniformity, The done

output had the particle size distribution of the aerosol pharmaceutical preparation prepared using the uniformity method of of ordinary stator / rotor type, and the same particle size distribution. The graphical representation of the mean particle diameter to the processing time of sieve DAIZA about this comparative example is shown in drawing 5. So that drawing 6 which plotted the balancer product particle diameter to the processing time of sieve DAIZA when operating sieve DAIZA by 55,158 kilopascals (8K psi) for uniformity may show, The triangle 6a expresses the CFC output prepared by sieve DAIZA, and the rhombus 6b expresses the CFC output prepared using the rotor / stator type homogenizer. When the already superfines-ized active ingredient is used, particle size distribution does not receive harmful influence with the homogenizer and the micronizer 12 which uniform. Rather, particle size distribution is substantially [as the time of using a rotor / stator type homogenizer] the same.

[0047](Comparative example 5) In order to superfines-ize the active ingredient which has not been superfines-ized, when the Micro fluidizer (registered trademark) of micro fluidics is used as a high voltage homogenizer and the micronizer 12, The particle size of the beginning of an active ingredient is reduced only 30% to the value which is equal to the value obtained about the aerosol pharmaceutical preparation at the time of using the superfines-ized active ingredient as a starting material. The particles which have the size within the limits of 12 (micrometer) to 15 micrometers (micrometer) were manufactured by this method. The graphical representation of the volume particle diameter of the average to the processing time of sieve DAIZA is shown in drawing 5. The round point 5a expresses the output prepared by sieve DAIZA using the active ingredient which has not been superfines-ized, and the rectangle 5b expresses the CFC output for commerce prepared using the rotor/stator. A particle size is beneficially reduced, when used for the homogenizer 12 uniforming when the active ingredient which has not been superfines-ized is used so that drawing 6 may show. Moreover, a particle size is not influenced by the rotor / stator type homogenizer use for uniformity. Although this invention was explained in relation to the specific embodiment, many modifications and modification should understand that it is clear to a person skilled in the art in the light of the above-mentioned explanation. For example, although the desirable embodiment of this invention is dispatched to the equipment and the method of uniforming the aerosol pharmaceutical preparation which used the HFC propellant, one ingredient may use the equipment and the method of this invention to the volatile mixture which has a low-boiling point. Therefore, this invention plans to include all the things of the modification included in the pneuma of the claim of Claims, and the range, and modification. As a result, reference document referred to on these Descriptions is applied.

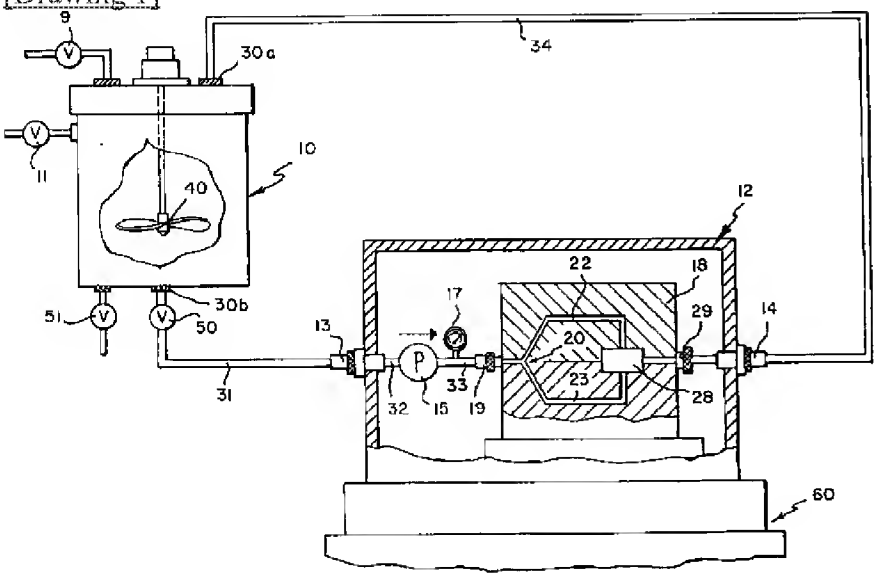
DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1]It is a schematic illustration of the closed continuation loop device by this invention.
[Drawing 2]It is a schematic illustration of the closed continuation loop device by this invention which carries out the bit of the aerosol pharmaceutical preparation into a container.
[Drawing 3]It is the schematic illustration of the closed continuation loop device by this invention which suited batch manufacture of the industrial scale.
[Drawing 4]It is the schematic illustration of the closed continuation loop device by this invention which suited the industrial scale which carries out the bit of the aerosol pharmaceutical preparation into a container.
[Drawing 5]In order to attain both uniformity of pharmaceutical preparation, and superfinesization, it is the graphical representation of the mean particle diameter to the processing time about the illustration pharmaceutical preparation containing the particles by which the active substance processed by the equipment by this invention is not ground beforehand.
[Drawing 6]Although uniformity of pharmaceutical preparation was attained, since superfinesization is not attained, it is the graphical representation of the mean particle diameter to the processing time about the illustration pharmaceutical preparation containing the particles by which the active substance processed by the equipment by this invention was ground beforehand.
[Explanations of letters or numerals]
9 Valve
10 Mixing vessel
11 An entrance with a valve
12 High voltage homogenizer
13 Entrance
14 Connector
15 High pressure pumping
17 Pressure surveillance gauge
18 Interaction room
19 Interaction room entrance
20 Flow splitter
22 and 23 Laminar flow
28 Impaction room
29 Interaction room exit
30 (a), 30 (b) connectors
30 (c), 30 (d), 30 (e), 30 (f) lead pipes
30 (g), 30 (h), and 30(i), 30 (j) lead pipes
30 (m), 30 (n), 30 (o), 30 (q) lead pipes
31, 32, 33, and 34 Lead pipe
40 Agitating equipment
50 Drain valve
51 Drain
60 Cooling method
70 Pump
80 Dispenser
85 Port

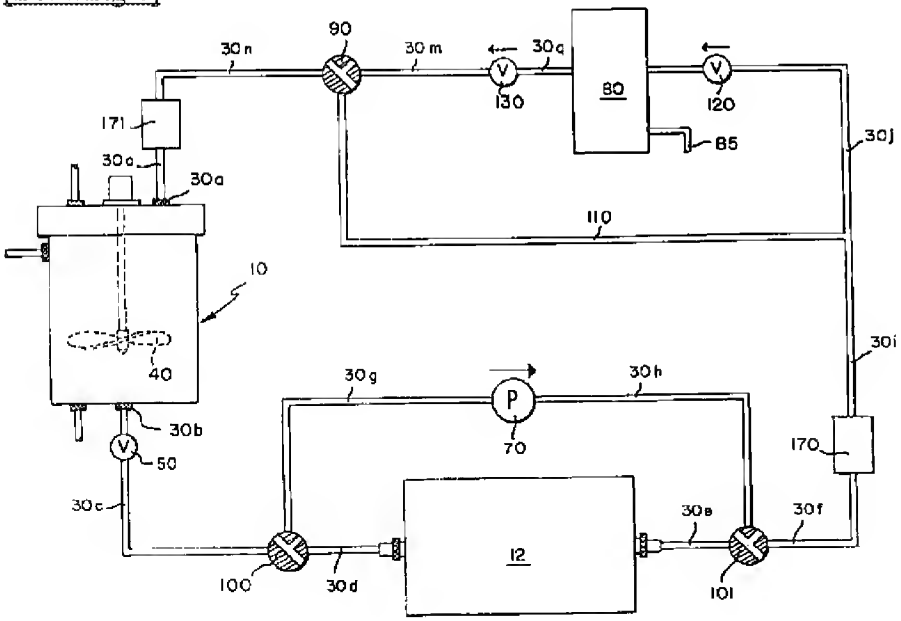
90 Pneumatic pressure bypass valve
100, 101 three way valves
110 By-pass line loop
120 Entrance check valve
130 Exit check valve
140 Pharmaceutical preparation container
150 Return-line valve
160 Return-line coupler
170 and 171 Serial flow instrument
180 Agitating equipment

DRAWINGS

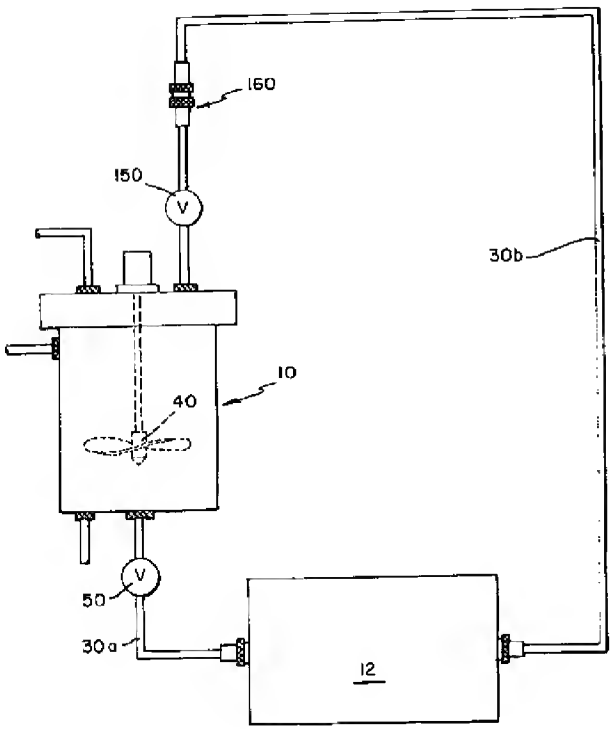
[Drawing 1]



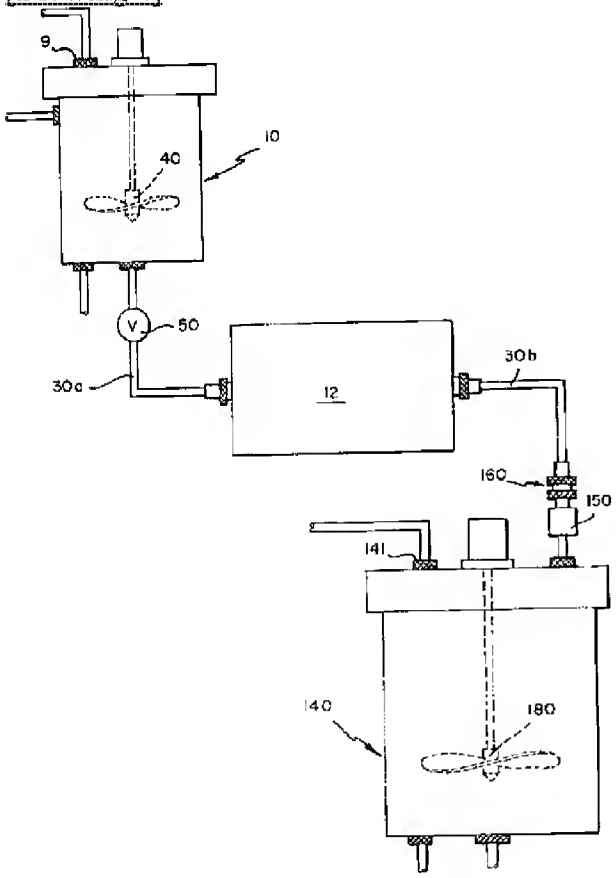
[Drawing 2]



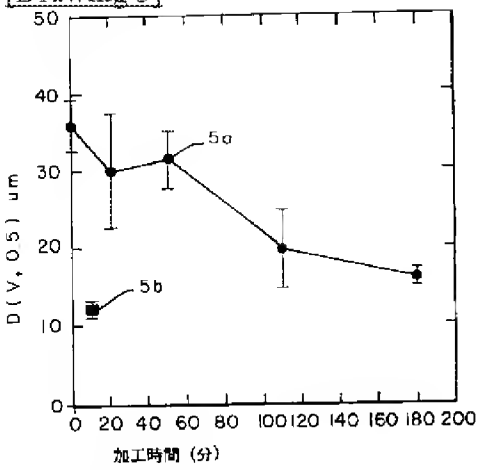
[Drawing 3]


160
150
V
30b
10
40
V
50
30a
12

[Drawing 4]


9
10
40
V
50
30a
12
30b
160
150
141
140
180

[Drawing 5]



[Drawing 6]